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I, Juha Tapani Silvanto, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Acknowledgements

At the end of my innings, I hope I may here be permitted to express my gratitude to Professor Vincent Walsh for providing a perfect wicket to bat on, and encouraging me to go for a six with every stroke, even if I might occasionally get caught at the boundary. I am equally grateful to Professor Nilli Lavie for improving my technique and for showing me that a boundary is more likely for a batsman who is aware of the field placements. During my four-year stay, I received from them the most cordial friendship and assistance. I must likewise take this opportunity of returning my sincere thanks to Professor Alan Cowey FRS who, during our collaboration involving experiments described in Chapters 4 and 5, showed me how to bat with style and effectiveness while treating the game with respect; this is indeed a gentlemen's game. To all three, I shall ever feel most thankful for the undeviating kindness with which I was treated.

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Sometimes he shakes his head in disbelief at what is happening. Here he is, an undistinguished graduate from a second-class university in the colonies, being permitted to address by first name men with doctorates in mathematics, men who, once they get talking, leave him dizzied in their wake. Problems over which he has dully wrestled for weeks are solved by them in a flash. More often than not, behind what he had thought were problems they see what are the *real* problems, which they pretend for his sake he has seen to.

Are these men so lost in the higher reaches of computational logic that they do not see how stupid he is; or – for reasons that are dark to him, since he must count as nothing to them – are they graciously seeing to it that he does not lose face in their company? Is that what civilization is: an unwhispered agreement that no one, no matter how insignificant, should be allowed to lose face?

- JM Coetzee, "Youth"

Abstract

This thesis investigated the role of cortico-cortical interactions and the role of striate cortex (V1) in human visual awareness in both normal subjects and the blindsight subject GY. In Chapter 3, the critical time windows of V1 and V5/MT activity in awareness of moving visual stimuli were compared using transcranial magnetic stimulation (TMS). The results demonstrate the importance of backprojections from V5/MT to V1 in awareness of real motion stimuli. In Chapter 4, the role of V1 in conscious perception of moving phopshenes induced by stimulation of V5/MT was studied. By varying the activation level of V1, it is shown that the amount of activity in V1 determines whether activity in V5/MT reaches awarereness. Furthermore, the activity in V5/MT influences the information content in V1, but it is V1 that determines whether that information reaches awareness. In chapter 5, it is reported that the blindsight subject GY can experience visual sensations, elicited by TMS, in his blind field. Importantly, such blind field percepts (phosphenes) could only be induced when GY's contralesional extrastriate area V5/MT was stimulated in close temporal proximity with the ipsilesional V5/MT. Stimulation of his ipsilesional V5/MT also altered to appearance of phosphene induced from the intact V1, but did not induce a blind field percept. The necessity of the contralesional stimulation in eliciting phosphenes from extrastriate cortex points to the importance of V1 in visual awareness. In chapter 6, the role of FEF in exerting top-down influences on the extrastriate visual cortex prior to eye movement preparation was studied. It was established, using TMS, that activity in the human frontal eye fields has a direct effect on the sensitivity of extrastriate visual area V5/MT, and that the spatial organisation of this top-down effect is lateralised in the human brain.

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Chapter 1: Literature Review

1.1. Definitions of awareness

If everyone knows what attention is (James, 1890), everyone certainly knows what perceptual awareness is. The richness of sensations created by our perceptual systems can hardly be denied, and their vital role as the window to the external physical word has since ancient times been a source of fascination to scientists and philosophers. With the rise of cognitive neuroscience, the neural mechanisms that give rise to these sensations have become a source of much debate. In the visual domain, this debate centers on "the neural correlates of consciousness" (NCC), a term introduced by Crick and Koch (1995), which they define as the "minimal set of neuronal events and mechanisms jointly sufficient for a specific conscious percept". In other words, the objective is to discover the neural basis of consciousness by isolating the neural activity which selectively correlates with that cognitive state. This paradigm is one of the cornerstones of cognitive neuroscience, and its application to the study of visual perception is by no means a novel approach, but the emphasis on consciousness has made Crick and Koch's new term attractive to many.

Defining a concept when "everyone knows what it is" has proved difficult in the past, and visual awareness is no different. Compounded with the scientific custom of breaking concepts into ever smaller and smaller pieces, it is no surprise there is no agreement of what constitutes visual awareness. In order to bring a number of definitions into one framework, Pollen (1999) has divided the concept of visual awareness into four components. The most basic of these, "phenomenal consciousness" (Block, 1995), refers to the minimal neural basis of the phenomenal experience of raw qualia such as brightness and colour; known as phenomenal NCC. The neural correlates of phenomenal consciousness can be considered to comprise a phenomenal perceptual space (Pollen, 1999), which does not enable detection of complex objects but it contains

the very features that makes vision so impressive. At this level, object localization is retinotopic and thus relative to the direct line of sight (Holmes, 1945).

The next component of visual awareness, as suggested by Pollen (1999), is an object recognition stage. At this stage the neural signatures of individual objects and concepts are encoded and can be used by working memory for further analysis at later stages. These representations may be symbolic, or alternatively, included into the phenomenal perceptual space.

A third stage involves the mapping of objects in locations of the external world in head-centered or body-centered spatiotopic coordinates (Gruesser & Landis, 1991; Andersen et al, 1985), providing a visual representation that is independent of our own spatial position (Gruesser & Landis, 1991). This *extra-personal space* subserves, amongst others, abstract representation of space (Andersen et al, 1985), and mental imagery of spatial mappings (Gruesser & Landis, 1991). These representations can modify but do not independently give rise to the experience of visual qualia.

The final component of awareness is referred to as the executive space (Block, 2005) and it involves planning and execution of voluntary motor acts. This "global workspace" also includes "consumer systems" such as memory, perceptual categorization, reasoning, and planning. Block makes a distinction between phenomenal contents of experience and access conscious content. The latter involves information that is made available to the "consumer systems"; in other words "broadcast in this global workspace". The neural basis of this information that is being sent to this global workspace is known as "Access NCC" (Block, 2005) – there are therefore two neural correlates of awareness one of phenomenal and another of access awareness.

It is the first of these, the "phenomenal consciousness" (Block, 2005), the phenomenal experience of raw qualia such as brightness and colour that the term "visual awareness" is used to describe in this thesis. Furthermore it will be the aim of this thesis to unravel at least some of the mechanisms that give rise to awareness of this kind.

1.2. Physiology of the visual system

1.2.1 The Striate cortex

Until the middle of the 19th century it was believed that that the cerebral cortex was only involved in intellectual functions, while thalamus was regarded as the highest sensory center (Carpenter, 1854). The first attribution of visual functions to the posterior cerebral cortex in was made by Panizza in the 19th century (described in Mazzarello & Della Sala, 1993), who studied blind stroke patients and carried out lesion studies on various species. The view that cerebral cortex was involved in sensory processes was supported by the identification of posterior cortex as the terminal for the geniculate optic radiation (Gratiolet, 1854). Subsequently the region of the stripe of Gennari was identified as the target of visual radations by Flechsig (1896); this region of the cortex was named "area striata" by Smith (1907).

In the human brain, the calcarine cortex, and later the whole striate cortex was identified as the "center of vision" or "cortical retina" by Henschen (1893) on the basis of over 160 cases of blindness and hemianopia after cortical lesions. He also found that the upper visual field is represented in the lower bank of the calcarine sulcus and the lower visual field in the upper bank. Point-to-point projection of the retinal image onto the brain had been proposed by Ibn al-Haytham already around the turn of the first century, and this was confirmed by Inoye (1909), who observed a correlation between the visual field defect and the locus of lesion in the striate cortex. Inoye also observed magnification of the representation of the fovea in striate cortex.

The organization and receptive field properties of V1 were first revealed by the single-cell recordings of Hubel and Wiesel in the cat (1962) and subsequently in the monkey (1968). Functionally, V1 is organized both vertically into columns and horizontally into layers. In vertical penetrations through the cortical layer, neurons have similar ocular dominance and orientation preferences, whereas the presence of simple (defined as

having "receptive fields with spatially distinct "on" and "off" areas separated by parallel straight lines), complex (no separation of receptive fields into excitatory and inhibitory parts) and hypercomplex (end-stopped) neurons is dependent on the horizontal layer (Hubel & Wiesel, 1962, 1968). Neurons in V1 are believed to play an important role in spatial frequency filtering and also act as filters for a number of other stimulus attributes that fall within its receptive field (e.g., Van Essen et al, 1992), such as colour, motion, and depth. V1 neurons can thus be considered as "general-purpose machines" that provide input to more specialized mechanisms in the visual system.

1.2.2. Extrastriate cortex

On the basis on the development of myelination, Flechsig (1896) divided the occipital lobe, into projection, intermediate, and terminal areas. The latter two were collectively named as "association cortex", as Flechsig believed that they became myelinated when children began to associate different senses with each other and with movement. In one of the earliest schemes of cortical sensory hierarchy, Flechsig proposed that the projection areas, later termed "visuosensory" and identified with the stripe of Gennari, obtained input from subcortical routes, and their output was to the intermediate, or "visuopsychic" areas that elaborated the visual image. This image could then be "associated" with other sensory modalitites in the terminal zone. The visuopsychic area was divided into parastriate cortex that was adjacent to striate cortex, and to an outer area, named peristriate cortex (Smith, 1907). These two areas corresponded to Broadmann (1909) areas 18 (now V2 and V3) and 19 (now roughly V4), and they were believed to be involved in perceptual and association functions rather than sensory functions, and by implication not retinotopically organised.

The key feature of extrastriate visual cortex is functional specialization. This was demonstrated by Zeki, who showed that nearly all neurons in the upper part of the posterior bank of the superior temporal sulcus, now known as V5 or MT, respond to visual motion but not to wavelength (Zeki, 1974). This finding was later confirmed by other studies (Van Essen et al, 1981; Albright, 1984). In humans, damage to the V5

homologue or TMS applied over this area has been shown to selectively impair performance in tasks requiring motion analysis, but other visual functions, such as contrast sensitivity and colour perception remain intact (Zihl et al, 1983; Newsome & Pare, 1988; Beckers & Homberg, 1992; Anand et al, 1999). It has also been shown that stimulating direction-selective neurons in this area biases the animal's behavioural response in direction discrimination tasks towards the preferred direction of the stimulated neuron (Salzman et al, 1990). The motion selectivity of V5 in human visual cortex has been demonstrated directly using positron emission tomography (PET) (Zeki et al, 1991).

The existence of a colour-selective visual area, V4, has also been proposed (Zeki, 1973, 1977), although the precise location of a "colour – center" in the human cortex is still a matter of controversy (Van Essen et al, 1981; Hadjikhani et al, 1998). In the inferotemporal (IT) cortex, further up the ventral processing stream, neurons are even more specialized, some being selective for complex geometrical figures (Tanaka, 1993). Furthermore, Perrett et al (1982) found that 10% of a sample of IT neurons responded twice as vigorously to faces than to any other stimulus of the same complexity, the level of responding being independent of the stimulus distance.

1.2.3. Antomical connectivity of the visual cortex

From the retina there are three parallel pathways to V1 (magno-, parvo-, and koniocellular), each characterised largely by the functional properties of retinal ganglion cells from which they originate. The M pathway arises from RGCs with large diameter axons that project to the two most ventral layers of the LGN (Leventhal et al, 1981; Conley & Fitzpatrick, 1989). These project primarily to layer 4calpha of V1 (and from 4calpha to 4B), with some weak projections to layer 6 (Hubel & Wiesel, 1972; Hendrickson et al, 1978). The magnocellular neurons are characterised by low spatial but high temporal resolution, high sensitivity to luminance contrast, lack of colour opponency, transient response profiles and fast conductance velocities (De Valois et al,

1966; Wiesel & Hubel, 1966; Schiller & Colby, 1983). The magnocellular stream projects dorsally from V1 to area to extrastriate regions V3, V3A, MT and MST, whereas the parvocellular pathway projects ventrally from V1 via V4 to inferior temporal cortex (Mishkin & Ungerleider, 1982; Mishkin et al, 1983; Ungerleider & Mishkin, 1982, Van Essen et al, 1985).

The smaller RGCs give rise to the parvocellular (P) pathway that projects to the four most dorsal layers of LGN. These project mainly to layer 4Cbeta in V1, with weaker projections to layers 4A and 6 (Hubel & Wiesel, 1972, Hendrickson et al, 1978, Blasdel & Lund, 1983). The parvocellular neurons are characterized by low temporal resolution, colour opponency, low achromatic contrast sensitivity and smaller receptive fields, allowing fine-detail vision (Wiesel & Hubel, 1966; Dreher et al, 1976, Kruger, 1977, 1979). Parvocellular RGCs are more numerous in the central retina, allowing them to convey more detailed spatial information, and they have colour opponent receptive fields that enable the detection of colour contrast. They also show sustained visual responses and have slower conducting velocities than receptive fields in the magnocellular pathway.

A functional hierarchy that divides the visual cortex into two processing streams has been proposed by Ungerleider and Mishkin (1982). In their model, the dorsal pathway, a system for spatial vision, projecting from V1 via V3 and V5 to the posterior parietal cortex, and the ventral stream, a system for object vision, projecting from V1 via V4 to the inferor temporal cortex. Their theory was based on suggestions that, both spatially and functionally, visual functions could be divided into identity (what?) functions and localisation (where?) functions (Schneider, 1967; Trevarthen, 1968)

1.2.4. Anatomical hierarchy

On the basis of their pattern of connectivity, the visual areas in the macaque can be placed into an anatomical hierarchy. The hierarchy relies on the principles that

connections between visual areas tend to be reciprocal in nature, and that within a reciprocal pair of connections, there tends to be differences in the laminar distribution of cells of origin and axonal termination (Maunsell & Van Essen, 1983a; Felleman & Van Essen, 1991). In this hierarchy, one type of projection arises primarily from cells in supragranular layers, with a small contribution of 10-15 % from infragranular layers, and terminates in the granular layer; this type of pathway was named feedforward (or ascending) projection. A second type of projection arises from cells in both supra-and infragranular layers and terminates most densely in layer I and/or VI. This type of pathway was named the feedback or descending projection. The hierarchy was constructed so that each area was assigned just above the highest area which provides an ascending input. Visual areas sharing intermediate projections were placed on the same level of the hierarchy. In this hierarchy (see figure 1.1), V1 is at the bottom of the six hierachical levels, with visual areas in the parietal, temporal and frontal cortex at the top. This hierarchy has been extended by Felleman and Van Essen (1991; see below).

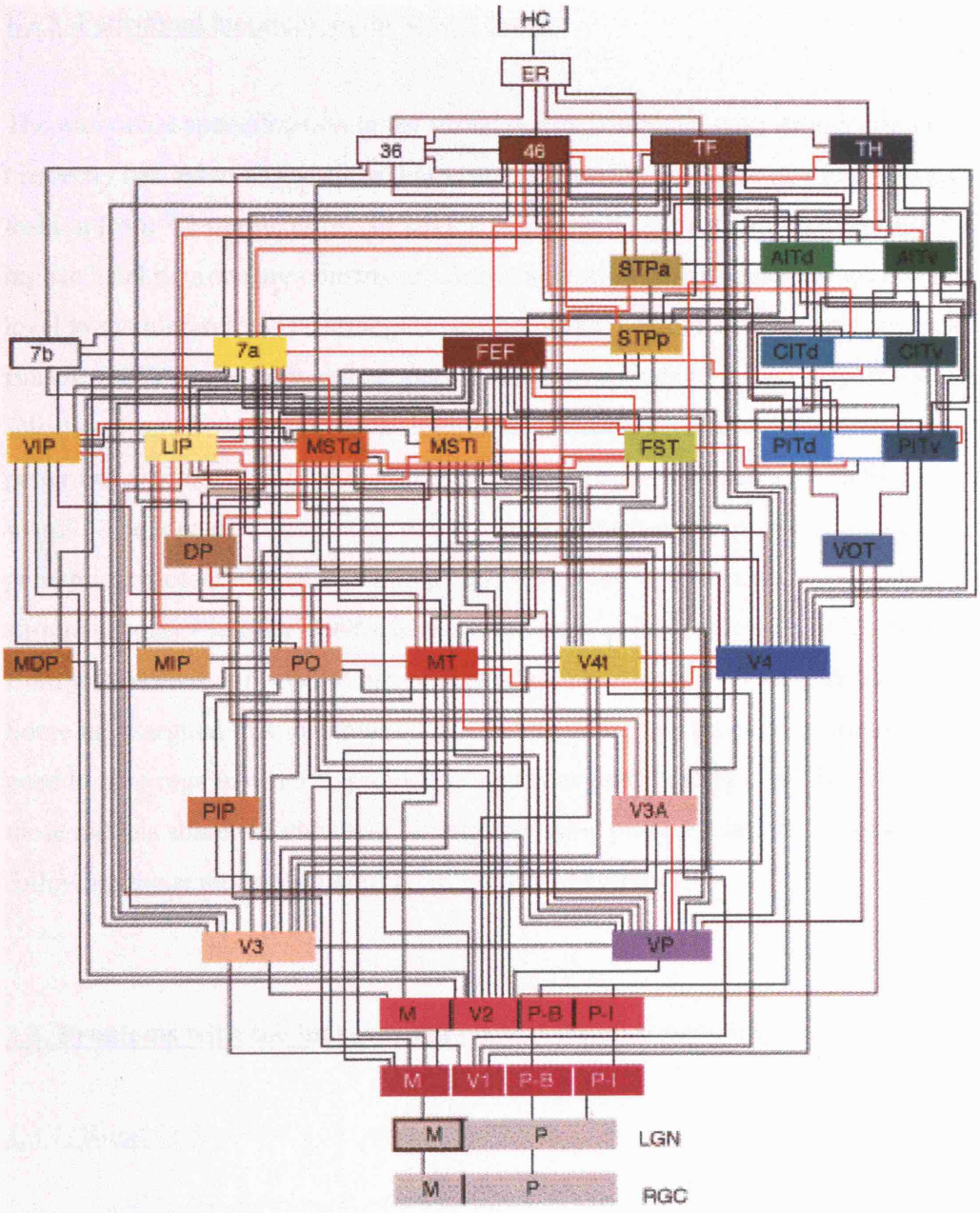


Figure 1.1. *The hierachical organization of the monkey visual system (from Felleman & Van Essen, 1991). V1 is the lowest cortical level of the hierarchy, extrastriate areas are at intermediate levels, and temporal, parietal and frontal regions at the highest level.*

1.2.5. Functional hierarchy in the visual cortex

The functional specialization in the visual cortex combined with its anatomical hierarchy has led to suggestions that visual processing proceeds in a feedforward fashion from V1 to the more specialized extrastriate neurons, and that the responses of higher-level neurons are constructed from the input from various neurons at a lower level in the hierarchy. The strongest version of the hierachical view was put forward by Barlow (1972), who argued that "perception corresponds to the activity of a small selection from the very numerous high-level neurons, each of which corresponds to a pattern of external events of the order of complexity of the events symbolized by a word". The idea of a one-to-one correspondence with the response of a neuron and perception is contradicted by findings that many neurons respond to multiple properties simultaneously (Schiller, 1996). The current view is that perception is likely to arise from joint activity of populations of high-level neurons (e.g., Young & Yamane, 1992). Some have argued that information processing in the two processing streams does not need to converge in order to provide a conscious percept (Zeki, 1978). Crucially, all these models share the view that visual processing proceeds in a feedforward fashion following the anatomical hierarchy of the visual system.

1.3. Problems with the hierarchical view of visual processing

1.3.1. Blindsight

The earliest systematic investigations into the effect of posterior occipital lesions concluded that field defects were absolute (Holmes, 1918). Some early investigations (Riddoch, 1917; Poppelreuter, 1917) suggested that motion perception could be selectively spared after striate cortex lesions, but subsequent studies showed that this was not the case in patients with complete V1 lesions (Teuber et al, 1960). However in some cases, when assessed through forced choice paradigms, the patient is able to detect stimuli presented in the blind field, despite reporting a complete lack of visual

experience. This above-chance level detection performance in the absence of visual experience is known as blindsight (Weiskranz et al, 1974). The first report of this phenomenon was by Poeppel et al (1973) whose sample of cortically blind patients was able to localize visual stimuli presented in their blind field at an above chance level with eye movements. Subsequently it was shown by Weiskrantz et al (1974) that patients with striate cortex damage can localize unseen stimuli also by pointing, and even more accurately so than by eye movements.

The localization performance of the unaware stimuli, assessed through forced-choice paradigms, is more accurate by pointing than by eye movements, implying that the visual processing of targets within the blind field cannot simply be attributed to oculomotor reflex (Weiskranz et al, 1974). Indeed, GY's ipsilesional V5 and V3 are activated by stimuli that he does not consciously perceive but that induce blindsight (Goebel et al, 2001). That extrastriate activation cannot be consciously perceived in the absence of a lower-order area is inconsistent with the hierarchical view of visual processing.

1.3.2. Visual response latencies

An implication of this hierarchical model is that visual response latencies of a given visual area can be predicted from its level in the hierarchy; areas higher up in the hierarchy should have longer latencies as a result of time required for the transfer of information from one level to the next. A direct comparison between onset latencies of single-unit responses at various levels of the hierarchy has been made, and the findings are inconsistent with this view. For instance, the frontal eye fields (FEF) placed at level 7 in the Felleman & Van Essen hierarchy, exhibit visual latencies comparable to those in level 2 (V2), level 3/4 (V3), level 5 (V5) and level 7 (MST). Furthermore, the latencies in all of these areas were, on average, only 6-9 milliseconds longer than the average V1 response. These results conflict with the view that information flow through the visual system follows the anatomical hierarchy. Routes that bypass some levels of the hierarchy have been suggested, for instance from V1 to V5 to FEF, but these have

not been taken into account when visual areas are assigned to different levels. Furthermore, that "higher level" areas such FEF are rapidly activated not only through cortico-cortical connections but also by subcortical input places the concept of "higher" and "lower" areas into further doubt.

1.3.3. Evolving functional roles of neurons

The assigning of hierarchy to the visual system is further complicated by the findings that the functional role of visual area is not constant throughout the neural response. In FEF there is an early response, 50-100 ms after stimulus presentation, to both undetected and detected visual targets, with the latter inducing slightly stronger activation (Thompson & Schall, 1999). In contrast, at latencies beyond 100 ms after stimulus presentation, there is a longer phase of activity that is associated with the monkey's perceptual report whether or not the target is actually there (Thompson & Schall, 1999). A similar shift in the properties of neural responses has been observed at the other end of the visual hierarchy, in V1. In response to a textured figure overlying a textured background, at 50 ms after stimulus presentation V1 neurons show selectivity for the local orientation of the line segments that make up the figure. At 80 ms the figure ground boundary selectively evokes a larger response than the rest of the scene, and at 100 ms the elements of the interior of the figure evoke a stronger response than the background elements (Lamme, 1995; Zipser et al, 1996). Importantly, this late stage of V1 activity, as is the late FEF response in the paradigm used by Thompson and Schall (1999), is correlated with the monkey's perceptual report (Super et al, 2001).

There is also evidence that in human subjects the activation level of early visual cortex is correlated with subjects' conscious percept rather than the physical attributes of the stimulus. Using fMRI Ress and Heeger (2003) found that, of subjects' responses in a contrast detection task, false alarms and not only hits were associated with higher level of activation in V1 (as well as in V2 and V3) than misses and correct rejections. That false alarms evoked more activity than correct rejections suggest that the activation

modulations were induced by the subjects' percept, as the physical stimulus was identical in the two instances.

Finally, normal responding of neurons in "lower" order areas such as V1 and V2 is dependent on feedback from anatomically higher areas. In the monkey, inactivation of V5 leads to a significant decrease in responses of V1 neurons to low salience bars moving against a static background and to a reduction of suppression of a moving background (Hupe et al, 1998; 2001). These findings suggest that backprojections from higher-order areas to V1 potentiate mechanisms of both the excitatory receptive field center (Sandell & Schiller, 1982) and of the inhibitory surround (Bullier, 2001). There is even evidence that feedback connections of the visual system are in some respects equivalent to the feedforward connections. Mignard and Malpeli (1991) have shown that feedback connections from V2 are able to maintain the orientation preference of cells in layers 2 and 3 of V1 when LGN input is blocked, implying that orientation selectivity in layers 2/3 of V1 can be derived equally from V2 and LGN.

It is not clear whether feedback connections play a role in all center-surround interactions that correlate with visual awareness, or whether their involvement is limited to specific cases. So far only two studies have directly probed the functional significance of feedback connections in human visual awareness. Cowey and Walsh (2000) attempted to induce phosphenes from intact extrastriate regions of the blindsight subject GY who had suffered an almost complete destruction of his left V1. He was able to perceive phosphenes induced from the contralesional hemisphere, but not when intact extrastriate regions in his ipsilesional hemisphere were stimulated. Furthermore, a control subject with blindness due to a subcortical trauma but with an intact V1 was able to perceive phosphenes. Pascual-Leone and Walsh (2001) studied the role of V1 in phosphenes induced from V5 in normal subjects. They applied TMS over V5 to elicit moving phosphenes and found that a TMS pulse delivered over V1, 5 to 45 milliseconds after V5 stimulation, degraded or removed the sensation of phosphenes. These studies demonstrate that not only does feedback from V5 modulate the neural responses to V1, as has been shown in single-unit studies, but that this process is

necessary for conscious perception of extrastriate activation. The fact that V5 phosphenes can be perceived at all suggests that cortico-cortical feedback can drive V1 neurons sufficiently to enable conscious perception, as in this case there is no LGN – V1 or V1-V5 feedforward activity.

The early functional significance of FEF, a higher level area in the anatomical hierarchy, and the late critical role of the lower order area V1 indicate that the neural processes that give rise to awareness are too complex to fit into a simple hierarchical model. The assignment of any kind of order, hierarchical or otherwise, is further complicated with the distinction of early and late stages of neural responding within a single visual area, and the significance of feedback connections to normal neural responding. Rather than searching for the magic area that produces awareness, it might be more productive to study the cortico-cortical interactions that induce the activation pattern of certain visual areas to correlate with, and perhaps even give rise to awareness.

4 .Theories of visual awareness

1.4.1. Zeki & Bartels (1999): Microconsciouness theory

In Zeki's and Bartels's (1999) microconsciousness theory, there is no region in the brain that constitutes a terminal stage in visual processing that determines whether a given pattern of activation reaches awareness. Instead, it is proposed that the brain consists of several functionally specialised units (or "nodes") in which awareness can arise in parallel. That is, each visual area that processes information acts also as a perceptual system that contains a neural correlate of awareness; for example, awareness of motion requires sufficient activation of areas that are functionally specialized in motion perception, most notably area V5. Similarly, perception of colour depends on activation of a colour specific region in the cortex. Furthermore, there is no distinction between processing and perceptual system; each cortical region that responds to visual input contributes directly to visual awareness. Despite this independence, each visual area is

nonetheless part of an extensive processing system that includes temporal, parietal and frontal cortices, and reciprocal connections between these and the visual cortex allow the former to modulate conscious perception. But despite the existence of this network it is the visual areas individually that determine whether awareness of the attribute that they are specialized for can arise.

How are different features are bound to create a unified and coherent picture of the visual world according to this model? Zeki and Bartels (1999) proposed two solutions to the binding problem. The first type of binding (generative binding) is hierarchical and always preconscious. This type of binding is equivalent to the feedforward sweep in that new receptive field properties are generated in higher visual areas from the combined input from lower-order areas as information is fed through the visual system. This does not answer the question of how activation of two areas that do not share feedforward connections are unified. This occurs through parallel binding, coupling of activity of cells possibly through synchronous or oscillatory firing, within an area or between visual areas. However as activity in each area has a conscious correlate, this binding is post-conscious. Any integration is therefore not necessary for the creation of conscious percept.

A key feature of this theory is that there is no one visual area that is of particular importance to conscious perception. Lesion to any given area should abolish awareness of the attribute that the lesioned area is selective for, but other attributes should still be consciously perceived. One case that is critical to the theory is that of GY, who has a complete lesion of V1 in his left hemisphere, but his ipsilesional V5 is intact. If there is a straightforward relationship between activation of an extrastriate area and conscious perception, as the theory predicts, despite the V1 lesion GY should still experience conscious percepts if these areas are activated. Barbur et al (1993) studied GY and came to the conclusion that "the subject was not only able to discriminate correctly the direction of motion of fast moving stimuli presented to his blind field but was also conscious of seeing it". Zeki and Bartels state that this is one the cardinal pieces of evidence in support of the microconsciousness theory. However GY himself has

always denied experiencing visual qualia in his blind field. When probed about his experiences in that particular study, GY said that "you never actually ever sense anything or see anything" (Weiskranz, 1997, p145). This theory will be tested by studying whether V5-V1 feedback connections are necessary for conscious perception of visually presented stimuli in the presence of V1-V5 feedforward activity, in addition to moving phosphenes (Pascual-Leone & Walsh, 2001).

1.4.2. Bullier's (2001) integration theory

Bullier's (2001) integrated model of visual processing is not concerned with how conscious perception arises. Rather, it attempts to explain how information across the visual scene can be integrated so that "global" properties such as shadows and lighting artifacts can be taken into account when the "local" aspects of the visual image are computed. In theory, this could be achieved with local horizontal connections within a single cortical area. However, reconciling the importance of such integration with the need for a high resolution image is problematic. This is due to the inverse relationship between cortical magnification factor and the size of the receptive field within a region. For instance, a V1 axon can reach a distance of only 0.6 degrees of visual angle and as a result, transmission of information over a distance of one degree visual angle through horizontal connections would take 100 ms. As 90 per cent of a neuron's output is transmitted within the first 100 ms of its response, it is unlikely that the integration takes place through horizontal connections in V1 (Heller et al, 1995).

Due to their larger receptive fields (at eccentricity of 10 degrees in the visual field, a motion selective V5 neuron might have a classical receptive field ten times larger than that of a V1 motion selective neuron; Albright & Desimone, 1987) and lower magnification factors, areas higher up in the dorsal and ventral processing streams are more capable of integrating information across long distances in the visual field. However, as higher visual areas are also more selective, this intergation can only involve a particular stimulus attribute. According to Bullier (2001) this leads to

problems when the visual stimulus requires integration of various attributes, such as colour, shape and depth, as the sparse set of connections between extrastriate visual areas makes it unlikely that this can be achieved by information exchange between them (Bullier, 2001).

According to Bullier's (2001) model, the problem of long-distance integration of various stimulus parameters can be solved by retroinjecting the global computations carried out by higher order areas through feedback connections into V1 and V2, where they guide the fine-detail analysis. The convergent nature of feedback connections means that they can carry information from long distances in the visual field and are therefore perfectly suited for guiding the fine-detail analysis in V1 (Angelucci et al, 2002). Furthermore, as input from the magnocellular processing stream reaches the visual cortex approximately 20 ms earlier than that conducted by the parvocellular stream (Nowak et al, 1995), it is perfectly suited for providing the initial global percept that guides parvocellular processing in V1. Furthermore, the characteristics of the magnocellular stream, such as high contrast sensitivity and larger receptive fields make it suitable for a fast, initial global analysis.

Bullier (2001) proposes that retroinjection of "global" computations from extrastriate areas back to V1 is a hallmark of normal visual processing, but it does not address the issue of what distinguishes conscious from non-conscious processing. In contrast, many have suggested that recurrent processing between numerous cortical regions is necessary for conscious visual perception.

1.4.3. Theories of recurrent processing

The idea that visual input is matched to an existing template was proposed in the 19th century by Helmholz, and it forms the basis of current theories on recurrent processing. The gist of this view in contemporary terms has been put forward by Grossberg (1976), who proposes that "sensory data activate a feedback process wherein a learned template,

or expectancy, deforms the sensory data until a consensus is reached between what the data "are" and what we "expect" them to be'.

It is the implementation of this process in the nervous system where differences between models arise. The importance of recursive or feedback loops in allowing sensory inputs to be compared against some criteria established within the nervous system was first proposed in a neural network model by Miller *et al.* (1960). These loops were proposed to recognize incongruities between the two in which case the network would continue to respond recursively until the incongruity vanished. Advances in understanding cortico-cortical back-projections (Kuypers *et al.*, 1965; Pandya and Kuypers, 1969) allowed further development of such models.

A key feature of this model was that the feedforward and feedback pathways leave mutually consistent trails of facilitated synapses in the complementary pathway (Milner, 1974; Pribram; 1974). Similarly, Grossberg (1976) proposes that select groups of neurons in a series of visual areas can establish a steady-state adaptive resonance (or reverberation), between regions if their patterns match, and suppress the reverberation if their patterns do not match. The models that will be discussed in more detail are those that specifically address the issue of extrastriate-striate feedback mechanisms in conscious visual perception.

1.4.4. Lamme et al (2000) feedforward/feedback account

The main premise of Lamme et al's (2000) account is that unconscious visuo-motor transformations, (as in blindsight), may be executed in an entirely feedforward processing cycle, while visual awareness is critically dependent on feedback connections to the primary visual cortex. As soon as a region has been activated by the feedforward sweep, recurrent interactions between neurons within that area and neurons that have been activated earlier at lower levels can begin. These interactions are mediated by horizontal connections and feedback-feedforward circuits between and within areas (Lamme et al, 2000). They are expressed as modulatory influences from

beyond the classical, feedforward, receptive field (Lamme & Spekreijse, 2000; Albright & Stoner, 2002).

The key difference between this model to that put forward by Pollen (1999) and Zeki and Bartels (1997) is that it is not activation within an individual visual area that gives rise to awareness. Even activation of "high" level areas in temporal, parietal or frontal cortex is insufficient to give rise to phenomenal visual experience. Instead, it is the recurrent interactions between areas, most notably between V1 and extrastriate areas, that allow visual input to reach consciousness. The main weakness of Lamme's theory is that it provides more of a description of experimental evidence rather than an attempt to explain it; no explanation is offered as to why feedback and not feedforward activity is necessary for visual awareness.

1.4.5. Hochstein & Ahissar (2002): Reverse Hierarchy Theory

The reverse hierarchy theory attempts to reconcile two observations on the nature of perceptual experience with the neural organization of the visual system. Firstly, it attempts to explain, in neural terms, the difference between rapid capture of global features of a visual scene with blindness to details and slower processing that enables access to the fine details of the visual scene. Secondly it tries to describe the neural process that differentiates conscious and attentive perception from implicit and automatic perception.

The difference between conscious and implicit visual perception is a functional division between two modes of processing, the former reflecting feedforward activity (as described by Lamme, 2001) and the latter is driven by focused attention and depends on feedback mechanism throughout the visual cortex. Specifically, conscious perception begins once a feedforward sweep has been completed and visual processing proceeds in a "top-down" fashion from the highest to the lowest cortical levels. Conscious perception in this view is a continuum of two modes, related to representations in the

reverse hierarchy top-down cascade of cortical areas. At one extreme is vision at a glance, with spread attention depending on the large receptive fields of higher cortical areas. At the other extreme is vision with scrutiny, which incorporates details available only in the small receptive fields at lower cortical areas. The reverse hierarchy theory therefore proposes that explicit visual perception follows the visual hierarchy in reverse direction, from top to bottom, with the attentional mode shifting from spread to focal.

The reverse hierarchy theory is successful in explaining many psychophysical results in neural terms. In relation to visual awareness, it is an attempt to relate the psychological distinction between conscious and implicit perception to an anatomical distinction between feedforward and feedback pathways. However while it states that "top-down attentional modulation" carried by the feedback connections is necessary for awareness, it does not describe the neural mechanism of this critical attentional effect, and in this respect fails to explain, in neural terms, why feedback activity but not feedforward activity gives rise to visual awareness.

Furthermore, there is also evidence that is difficult to link with the view that conscious perception is a continuum between global perception enabled by areas "high" in cortical hierarchy and the perception of local details that require "lower-order" areas with small receptive fields. The problem is that the "lowest" of all areas, V1, appears to be necessary not merely for the conscious perception of fine details, but also of large, global percepts induced by TMS applied over the extrastriate cortex; phosphenes cannot be induced from the extrastriate cortex in the absence of V1 (Cowey and Walsh, 2000). Imaging studies have shown that fronto-parietal areas associated with attentional control are intact in GY, and there is no reason why these could not modulate GY's intact extratriate areas in a top-down fashion to enable conscious global percepts to arise in the absence of V1.

1.4.6. Pollen's recurrent model (1999)

Pollen's (1999) theory could be considered as compromise between the modular (Bartels & Zeki, 1998) and recurrent models (Lamme, 2001; Hochstein & Ahissar, 2002) of visual awareness. It was also the first theoretical framework to propose that re-entry of information to lower visual areas is necessary to visual awareness. Pollen's theory is an attempt to accommodate the findings that V1 is indispensable to visual awareness, but that its activation is insufficient to generate a percept if the integrity of regions such as the parietal cortex is disrupted, as is shown by the neurological conditions of visual hemineglect and simultanagnosias. This is accomplished through feedforward and feedback pathways that link visual areas together into a recursive loops.

All visual areas in the ventral processing stream from V1 through the inferotemporal cortex and to temporal areas serve as possible substrates for different aspects of phenomenal visual experience; this view of modularity of conscious visual perception is similar to Zeki's (1997). The difference to Zeki's view is that the totality of phenomenal experience may require multiple, near-simultaneously experienced percepts in different cortical areas even within a common modular function such as luminance processing. For conscious perception to arise, a consensus needs to be reached between the visual areas that process a particular stimulus; this is achieved through feedforward and feedback pathways linking multiple cortical areas; conflicts of information prevent conscious perception of that stimulus. Synchronous neuronal activity on a short timescale within and across cortical areas may also serve as a marker that a "steady state" (or consensus) has been achieved, and is therefore a correlate of awareness.

In Pollen's (1999) model, V1 and V2 provide respectively the fine-grained and medium-grained representations in the luminance domain. In contrast, phenomenal experience of complex objects over wider expanses of two-dimensional space and of three-dimensional representations of the visual world may well depend upon computations begun in V4 (Merigan and Pham, 1998) and perhaps completed within the temporal

lobe. Therefore, which visual area mostly correlates with a phenomenal experience depends on the stimulus that is tested.

1.5. Objectives of the present thesis

The objective of experiments described in Chapter 3 was to determine whether backprojections from V5 to V1 are necessary for conscious perception of real motion stimuli. The necessity of such backprojections has been demonstrated with moving phosphenes induced from V5, but whether this mechanism applies to visually presented motion stimuli is an open question. This is an important issue because it is possible that feedback to V1 is particularly important in situations when the feedforward activity in V1 has been bypassed, as is the case with moving phosphenes in the experiment by Pascual-Leone and Walsh (2001). It could be the case feedback to V1 from extrastriate areas is less critical when feedforward activity is allowed.

In Chapter 4, the objective was to determine whether activation level of one site in the extrastriate – V1 feedback loop is particularly critical in dictating the presence of awareness. Specifically, it will be determined whether the activity level in both sites in the V5-V1 feedback loop determines the presence and content of awareness, of whether either site is more critical than the other.

The experiments described in Chapter 5 studied the neural basis of visual awareness in the blindsight patient GY. The objective was to study whether GY's contralesional visual cortex can enable conscious perception in GY's blind field, and if so, through which mechanisms.

Cortico-cortical interactions of course have roles in many, if not all, sensory and cognitive functions and in this thesis I have mainly explored the interaction between V5 and V1 in neurologically normal subjects (Chapters 3 and 4) and in a patient with damage to V1 (chapter 5). As described above, the frontal eye fields (FEF) have also

been associated with visual awareness, and the experiments in Chapter 6 investigated the influence of FEF on extrastriate activity. Specifically, the ability of FEF to modulate visual awareness through enhancements of neural sensitivity in V5 was studied.

Chapter 2: General Methods: Transcranial magnetic stimulation

2.1. The basis of TMS: the principle of electromagnetic induction

The first evidence on the relationship between magnetism and moving charges in 1819 was discovered by Hans Christian Oersted who discovered that a moving electric charge creates a magnetic field around it, and that a coil carrying a steady current can exert a constant magnetic force on a second coil. However, if the current in one coil changes, the flux through the second coil changes as well; this can induce a current in the second circuit. This principle of electromagnetic induction was discovered by Michael Faraday in England and Joseph Henry in the United States who demonstrated that a moving magnet near a conducting loop can cause a current in the loop. The changes in magnetic field induce circulating currents called eddy currents in conducting materials. This is the phenomenon that enables a car battery to start the engine, and a TMS coil to excite brain activity.

2.2. History of TMS

The first use of magnetic fields to influence brain activity was accomplished in the 19th century when the French physician Arsene d'Arsonval (1896; cited in Walsh & Pascual-Leone, 2003) used the technique to induce the sensation of flashing lights, phosphenes. Similar experiments were carried out in England where Thompson (1910) constructed a coil that induced sensations that covered the whole region of vision with "faint flickering illumination, colourless or of a slightly bluish tint", which could be perceived with eyes open and in daylight. The first moving phosphenes were reported by Magnusson and Stevens (1911), who found that such percepts could be induced when the direct current was being initiated or arrested, but not when the direct current was flowing. These are precisely the conditions in which eddy current can be induced in a

conducting material and are therefore expected to produce the strongest perceptual consequences.

As the stimulating coils used in the early experiment were large in size, whether the phosphenes were induced by stimulation of the retina rather than the occipital cortex could not be determined. Some thirty years later it was demonstrated that stimulation of either site can induce a clear phosphene: Walsh (1946) and Barlow et al (1947) induced phosphenes by placing the coil near the temple (suggesting a retinal origin) and Kolin et al (1959) demonstrated that phosphenes can be induced both when the coil is placed against the occipital cortex or the temple. This was not their only contribution to the field of magnetic stimulation: by isolating a frog sciatic-nerve-gastrocnemius-muscle preparation and looping the sciatic nerve around the pole of the magnet, Kolin et al (1959) also provided proof that magnetic fields can be used stimulate nervous tissue in vitro.

In 1965, Bickford and Fremming used a pulsed magnetic field to twitch skeletal muscle in intact frogs, rabbits and humans. Their technique was notable as, instead of sinusoidal alternating current to power the excitation coils, they discharged capacitors into the excitation coil to produce a single, short duration current waveform. This method resulted in a single twitch when a motor nerve was stimulated and it is the technique that is used in TMS research today. The critical demonstration that stimulation of the human cortex produces a measurable effect was provided by Barker (1985), who applied TMS over the motor cortex to induce twitches and recorded the resulting EMG activity from intrinsic hand muscle.

2.3. The physics of TMS

In TMS, electric current is used to induce a magnetic field with the objective of altering local electric fields in the brain; the magnetic field passes through the scalp and the skull of the subject inducing current that stimulates neural tissue. The stimulation induces an electric field both inside and outside the axon (Nagarajan, Durand

&Warman, 1993), creating a transmembrane potential, or a nerve depolarization voltage (Rudiak & Marg, 1994). This transmembrane potential can cause membrane depolarization and the initiation of an action potential, which then propagates along a nerve like any other action potential. However, this is not a guaranteed outcome. If the induced field is uniform across the cell membrane, no current will be induced. The axon must be bent across the electric field or the field must traverse an unbent axon. The efficacy of TMS in stimulating neural tissue therefore depends on both the orientation of the stimulating coil and the orientation of the underlying nerve fibres.

The principle of electromagnetic induction states that in addition to the magnitude of the magnetic field, its rate of change determines whether current is induced into the conducting material. To fulfill both requirements, in a typical TMS system a capacitor charged to a high voltage (normally 8kA) is discharged into a stimulating coil with a very short rise time (appr. 0.1-0.2 ms), with the overall duration of the pulse being less than 1 msec (see Figure 2.1.). The rise time of the pulse is of great importance because the faster the rise to peak intensity of the magnetic field, the less time there is available for the neural tissue to lose charge. For this reason the waveform of the TMS pulse is central to its efficacy. Indeed, a biphasic waveform has been reported to require lower field intensities to induce a current in neural tissue than a monophasic one, as the former has a faster rise time. In addition to the induction effect from the current of the coil, a negligible accumulation of charge on the scalp contributes to the induced field (Roth et al, 1991).

The most focal effect of TMS are obtained using a figure-eight coil (Ueno, Tahsiro & Harada, 1988), which consists of two circular coils that carry current in opposite directions. The electric fields summate at the center of the coil where the two circular components meet. The best focality can be achieved by placing the center of the figure eight coil on the optimal stimulation site. Because the wings of the figure-eight coil are several centimeters above the scalp, they are unlikely to induce an effective magnetic field. The depth of stimulation cannot be known conclusively, but one estimation is that for the standard-figure eight coil, stimulation 4 mm below the coil will cover an area of

approximately 7 by 6 cm, which decreases to 4 by 3 cm at 20 mm below the coil (Barker, 1999). As the latter approximately corresponds to the cortical surface, it is clear that TMS can only be used to study regions that are close to the cortical surface. The focality of a circular coil can be increased by using only one section of its arc to make contact with the scalp.

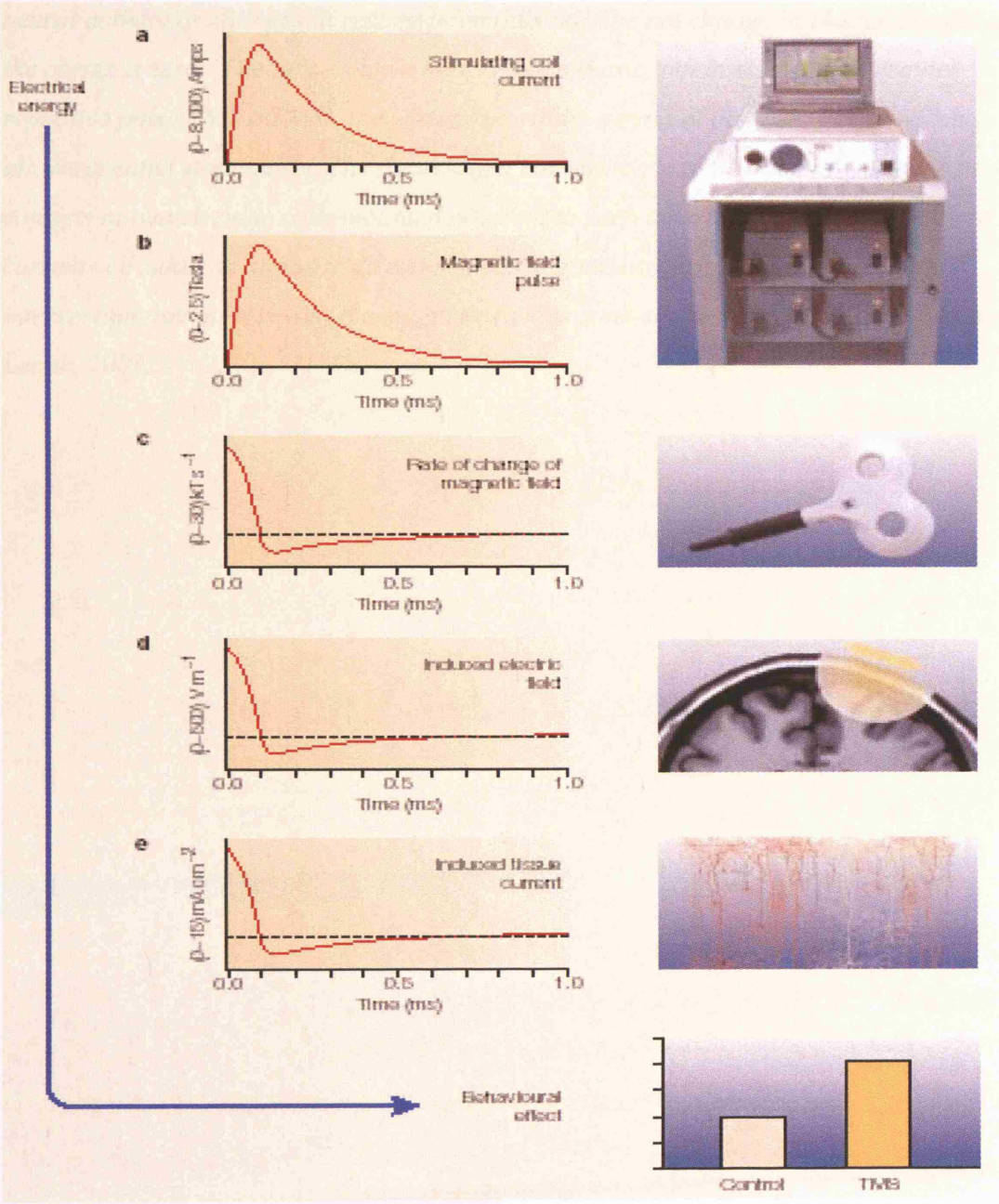


Figure 2.1.: Transcranial magnetic stimulation. *An electrical current of up to 8 kA is generated by a capacitor (a) and discharged into a circular, or figure-of-eight shaped, coil which in turn produces a magnetic pulse of up to 2 T (b). The pulse has a rise time of about 0.2 ms and a duration of 1 ms and owing to its intensity and brevity changes at a rapid rate (c). The changing magnetic field generates an electric field (d) resulting in neural activity or changes in resting potentials (e). The net change in charge density in the cortex is zero. The pulse shown here is monophasic, but in studies that require repetitive pulse TMS (rTMS), the waveform will be a train of biphasic pulses which allow repeated stimulation. The figure-eight coil, which is most commonly used, consists of two circular coils mounted adjacent to each other in the same plane. Their currents circulate in opposite directions, causing the two fields to summate at their intersection, and as a result, the magnetic field is cone-shaped (from Walsh & Pascual-Leone, 2003).*

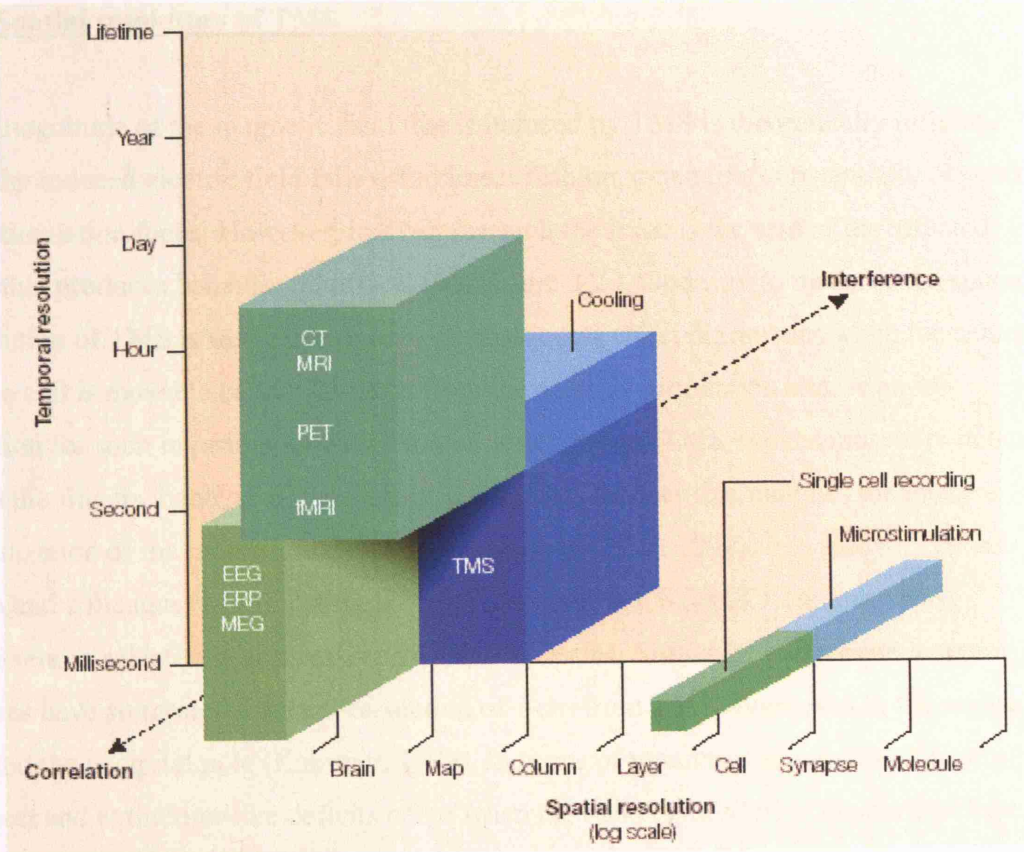


Figure 2.2: Spatial and temporal resolution of TMS.

The place of TMS in neuropsychological studies is best thought of as the 'problem space' it occupies. This figure shows the spatial and temporal resolution of TMS compared with other techniques. However, it is not just the spatial and temporal selectivity that make TMS a useful experimental approach; it is the ability of TMS, like cooling and microstimulation, to transiently interfere with brain functions. In contrast, existing neuroimaging techniques provide correlative data. Clearly, when one selects a technique, one is also making a selection about the kind of question one can ask. CT, computerized tomography; EEG, electroencephalography; ERP, event-related potential; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography. (from Walsh & Cowey, 2000).

2.4. Spatial resolution of TMS

The magnitude of the magnetic field that is induced by TMS is theoretically infinite, and the induced electric field falls off in linear fashion, extending substantially beyond the stimulation focus. However, in TMS research the issue is the size of the affected area that produces behavioural effects (see Figure 2.2.). One way to measure the spatial resolution of TMS is to determine how a behavioural effect diminishes when the center of the coil is moved a certain distance from the optimal stimulation site. A good location for such investigation is the motor cortex, where TMS evokes muscle twitches from the fingers, hand, arm, face, trunk and leg in a manner that matches the gross organization of the motor homunculus (Wassermann et al, 1992). In a study by Brasil-Neto and colleagues (1992), stimulation of sites between 0.5 and 1 cm apart was sufficient to selectively activate each of these muscles. Similarly, phosphene mapping studies have suggested a spatial resolution of 1 cm from TMS when used in the region around the occipital pole (Kammer, 1999). In terms of measures of cognitive function, neglect and extinction-like deficits occur when the coil is placed over the parietal lobe, but the effects quickly decays when the coil is moved few centimeters away from the optimal stimulation site (Ashbridge et al, 1997); this allows the posterior parietal cortex to be localized using a functional method in which the TMS coil is moved around the posterior cortex until a site is found from which neglect-like deficits can be obtained.

Direct evidence on the spatial resolution of TMS has been obtained from studies that have used brain-imaging techniques to measure the extent of TMS effects. Wassermann et al (1992) mapped the cortical representation of a hand muscle with TMS and coregistered the inferred volumetric fields with anatomical MRIs from each subject and with PET images obtained while subjects moved the finger that had been mapped with TMS. The outcome of these two mapping methods was within 5-22 mm of one another.. However, a concern in this study is that the hand area lies deep in the central sulcus, and therefore its actvation by TMS might occur trans-synpatically rather than directly, as is suggested by comparisons of EMG latencies elicited by TMS and electrical stimulation (Day et al, 1987, 1989, Amassian et al, 1990). These studies have shown that

magnetically evoked latencies are approximately 1-2 msec longer than electrically evoked ones.

Paus and colleagues (1997, 1998, 1999) have addressed the issue of focality by studying the PET activation of TMS over the frontal eye fields that were localized on the basis of subjects MRI images. They found that TMS has a major effect under the center of the coil and secondary effects at anatomically connected sites, such as the parieto-occipital region in this case. That the effect of TMS is highest is directly underneath the center of the coil has also been shown using fMRI (Bohning et al, 1999). By using TMS in combination with EEG, Ilmoniemi et al (1997) found that the effect of a TMS pulse applied over the motor cortex spread to immediately adjacent cortical areas within 5-10 milliseconds and to the homotopic regions in the contralateral hemisphere within 20 milliseconds. Whether this weaker distal activation leads to behavioural effects depends on the behavioural paradigm.

2.5. Temporal resolution of TMS

The duration of a TMS pulse is brief, approximately 1 millisecond, but its effect on single-neuron level have been measured to last for hundreds of milliseconds and even seconds (Moliazde et al, 2003). However, the critical issue in most TMS experiments is the duration of the TMS effect as reflected in behavioural effects. Brain regions are often critical to a certain cognitive process for a limited duration and the question is, how precisely TMS can be used to determine this critical time window. This can be studied by applying single pulses of TMS at various time windows after the onset of the stimulus. In the classic study by Amassian et al (1992), discussed in more detail below, single pulses of TMS applied over the occipital lobe disrupted performance in a letter detection task when applied within a 20-30 ms time window in most subjects. A similar temporal specificity with TMS applied over the occipital lobe has been reported by Corthout et al (1999). Others have reported temporal time windows of 40 ms in which TMS can disrupt behaviour when applied over the angular gyrus (Ashbridge et al, 1997)

and dorsal premotor cortex (Schluter et al, 1999). With its high temporal resolution, TMS is ideal not only for determining the critical time window in which a cortical area is necessary in a given cognitive process, but also for exploring cortico-cortical interactions.

The duration of TMS effects depend on the stimulation parameters. In experiments investigating cognitive processes with an extended temporal profile (i.e. processes that last for hundreds of milliseconds or even seconds, such as spatial attention, e.g. Hilgetag et al, 2001), a high temporal resolution is not of essence. To study such processes an offline TMS procedure can be used to induce a long-lasting suppression in cortical excitability. In this procedure, low frequency (normally 1 Hz) for a long time period (10 to 20 minutes) can induce suppressive effects that last for half of the duration of the stimulation period (Thut et al, 2003).

2.6. TMS as a "virtual lesion" method

TMS is a technique that can be used to disrupt brain activity and it can therefore be used to determine the necessity of a cortical region in a given cognitive process. This provides an advantage over other non-invasive techniques such as functional magnetic resonance imaging and EEG which can be used to demonstrate correlations between brain activity and behaviour, but cannot be used to infer necessity.

TMS has three major advantages over studying brain-damaged subjects when investigating the necessity of a brain region in a given cognitive function. Firstly, due its high temporal resolution, TMS can inform not only *whether*, but also *when* a brain area is necessary. In other words, it can reveal the critical time windows of cortical regions in cognitive functions. This information cannot be obtained by studying brain-damaged subjects. Secondly, brain lesions are rarely limited to one cortical region, which can lead to difficulties when the objective is to distuinguish the functions of cortical areas that are close to each other. This is less of a problem in TMS research, due to the good spatial resolution of the technique. Thirdly, in brain-damaged subjects

considerable inter-and intracortical plasticity occurs over time whereas the "lesions" induced by TMS are transient and neural re-organisation therefore is not normally an issue.

How should the disruptive effect of TMS on cognitive processes be conceptualized? The general consensus is that TMS adds noise to neural information processing (Walsh & Pascual-Leone, 2003). This is because TMS stimulates neurons in random, whereas a hallmark of successful information processing is a highly organized pattern of neural activity. In this sense, behavioural deficits induced by TMS can be thought to be due to a decrease in the signal-to-noise ratio.

2.7. Safety issues

The welfare of subjects is paramount in TMS experiments. The main safety risk in TMS research is the possibility of seizures, a rare but a serious risk. For this reason subjects with a family history of epilepsy should not take part. Guidelines on the safety limits of stimulation parameters such as frequency, intensity and duration (Wassermann et al, 1998) were closely followed in all work reported in this thesis. Furthermore, all subjects were screened for factors that increase the risk of seizures (such as insufficient sleep and alcohol withdrawal) and informed consent was always obtained. All the reported experiments were approved by the ethical board of University College London.

2.8. TMS studies of visual cognition

2.8.1. Amassian's early studies

Since the classic studies of Amassian et al (1989, 1993), TMS has been a useful too for studying the neural basis of visual perception. In their first set of studies, subjects were presented with trigrams of randomly chosen letters that were briefly presented at fixation. Single-pulses of TMS were applied over the calcarine cortex (2 cm above the inion at midline) at time windows ranging from 0 and 200 ms after stimulus offset.

When TMS was applied 80 -120 ms after stimulus onset, subjects' ability to detect the letters was impaired. Furthermore, in what was the earliest demonstration of the focality in TMS studies of visual perception, Amassian et al (1989) demonstrated that when the coil was moved slightly laterally, most disrupted were letters that fell into the contralateral hemifield. In a subsequent study, Amassian et al (1993) were able to facilitate visual detection in a visual-masking paradigm by applying TMS over the same occipital location 80-100 after the mask had been presented. The mechanism in both instances is the same, but depending on whether TMS is applied at a critical time window relative to the processing of a target or a distractor, TMS can be used to either disrupt or facilitate performance. The work of Amassian et al (1989, 1993) demonstrated not only the ability of TMS to induce robust disruptions to visual perception but it also its ability to unravel the time course of visual processing.

2.8.2. Studies on motion perception

The first attempts to disrupt motion perception using TMS was carried out by Beckers and Homberg (1992), who asked subjects to discriminate the direction of a random-dot motion pattern placed into the left or right visual field 4 to 6 degrees from fixation, which was moving either to the left or right. They found that stimulation of a site 4-6 cm to the right or left of mid-sagittal plane (the region of V5/MT) had a strong disruptive effect on subjects ability detect motion direction in the contralateral (but not in the ipislateral) hemifield. The disruption was larger when the left hemisphere was stimulated and when the motion was towards periphery rather than towards the fixation. Performance on a colour perception task was unaffected by stimulation of this site, demonstrating the specificity of the TMS effect on motion processing. Stimulation of mid-occipital cortex, which Becker and Homberg (1992) referred to as V1, induced only a moderate impairment into that was not hemifield specific. However, this stimulation site was 5 cm above the inion and it is more likely to correspond to the V3/V3A region rather than V1/V2 region. Subsequent studies have found comparable disruptive effects on motion perception resulting from V1/V2 and V5/MT stimulation (e.g., Hotson & Anand, 1999).

Using a stimulus of a much shorter duration (3 frames presented for a total 50 ms) that moved in one of the four cardinal directions, Hotson et al (1994) studied the effect of TMS applied over the "temporo-occipito-pareital region" in the left hemisphere (approximately the same lateral site as stimulated by Beckers & Homberg, 1992). The stimulus was presented either in the left or right hemifield at an eccentricity of 10 degrees from fixation. Strongest disruptions were obtained 100-150 ms after stimulus onset, and disruptions were observed for motion in both hemifields. A small reduction in performance was also observed in a spatial acuity test, perhaps suggesting that coil was not optimally over V5/MT or that use of circular coil also disrupted surrounding cortical areas. When a figure-eight coil was used, the effect on motion discrimination induced by stimulation of left hemisphere was larger on the right hemifield. Subsequent studies, using variations of stimuli described above, have used TMS to disrupt motion detection and direction discrimination with TMS (Beckers & Zeki, 1995; Matthews et al, 2001).

2.8.3. Correspondence between coil location and retinotopy of visual field defects

Kastner et al (1998) studied the retintopy of transient field defects induced by TMS over various locations around the occipital pole and found that when the lower end of a circular coil was placed 2 cm above the inion, all targets presented within 1 degree remained undetected, and most targets 4-9 degrees lower field were also missed. When the coil was moved down so that its lower end was above the inion, the central 1 degree remained invisible but stimuli in the lower visual field at eccentricities of 4-9 degrees were now detected. At a position of 4 cm above the inion, the upper visual field within the central 1 degree was spared, but the lower field was still disrupted. Shifting coil laterally resulted in a field defect in the contralateral, lower visual field.

Within the central 1-3 degrees, the visual field deficits covered both the lower and upper visual field, whereas at eccentricities beyond 3 degrees only the lower visual field was affected. The former is consistent with the retinotopic representation of V1 where

the upper and lower visual field representations lie close together and are not split by the horizontal meridian (Holmes, 1918). The peripheral deficits, however, are unlikely to reflect V1 activation, as the visual field representation of V1 beyond 5 degrees is buried deep within the calcarine sulcus.

Instead, the deficits restricted to the lower visual field are more likely to reflect activation of V2/V3. This is because the lower visual field representation of V2/V3 for eccentricities between 3-25 degrees lies on the lateral surface of the cortex above the calcarine sulcus (Sereno et al, 1995), and is therefore accessible to TMS, whereas the upper field representation (ventral V2/V3), lieing below the calcarine sulcus, is not. That the deficit induced by TMS never crossed the horizontal meridian is consistent with the fact that nearby points below and above the HM are represented in ventral and dorsal V2 at topographically widely separate locations (Van Essen & Zeki, 1978, Horton & Hoyt, 1991), as is apparent in isolated lesions of V2/V3 which respect the horizontal meridian (Horton & Hoyt, 1991). This visual field deficit is unlikely to be result from stimulation of the optic radiation, as the only location where these fibres are separated with a split of the HM is at the level of the posterior horns of the lateral ventricles (Spalding, 1952; Harrington & Drake, 1990). This is 3-4 cm away from the scalp and therefore unlikely to be affected by TMS.

2.8.4. Phosphenes

Stimulation of visual cortex can disrupt visual processing but it can also induce a positive effect: the perception of phosphenes. The neural basis of these two phenomena is the same. TMS over visual cortex activates neurons as does visual input from the retina, and if the activation level is high enough, a phosphene is perceived. If the activation level induced by TMS is too low to induce a phosphene, a population of neurons will nevertheless have been activated. If this activation coincides with the incoming visual information that under normal conditions give rise to a highly organized pattern of neural activity, the random neural activity will, as discussed above,

decrease the signal-to-noise ratio of that activity. This is reflected as an increase in visual detection thresholds (Kammer & Nusseck, 1998). While TMS can increase visual detection thresholds, presentation of a visual stimulus can increase the level of stimulation required to induce a phophene: if subjects are viewing a visual stimulus (as opposed to a dark background), the intensity of stimulation required to induce a phosphene is increased (Rauschecker et al, 2004). This implies that the patterns of neural activity induced by TMS and a visual stimulus are in competition with each other.

One of the first systematic explorations on correspondence of coil location and phosphene perception was carried out my Marg and Rudiak (1994). As in most of the early studies, a circular coil was used, with one edge placed on the scalp. With this technique there is an issue of focality, but their main observations still hold. Bilateral phosphenes were induced when when the edge of the coil was placed on the midline, while moving it slightly laterally confined the phosphene to the contralateral field. Moving the coil up along the midline moved phosphene down and into the periphery. Phosphenes could be induced when the coil was moved upwards along the scalp at locations up to 10 cm from the inion.

2.8.5. Correspondence between visual field defect and phosphenes

Kastner et al (1998) reported that whereas stimulation around midline induced foveal phosphenes, moving the coil to either side moved the phosphene to the contralateral hemifield, corresponding with the topography of the visual field defects that they reported. However, they did not study this correspondence systematically. This was done by Kammer (1999) who applied TMS within a 2 x 2cm region of cortex around the inion and studied the visual field at eccentricities ranging up to 10 degrees of visual angle. Instead of using the round coil, as was done by Kastner et al (1998), a figure-of-eight coil (10 cm) was used. In addition to demonstrating the topographic correspondence between phosphenes and visual field deficit induced from a specific region of cortex around the inion, Kammer noted that the size, form and site of the

phosphene were highly reproducible from a given stimulation site. This is yet another demonstration of the focality of TMS.

As was discussed above, the visual field deficits that result from stimulation of a given region of scalp near the inion are restricted to small segment of the visual field. And as the relationship between superficial (such as the inion) and cortical landmarks (such as the calcarine sulcus) vary widely amongst subjects, the placement of the coil could be difficult without access to MRI images of each subjects. A way to circumvent this problem is to make use of the topographical correspondence between phosphenes and visual field deficits, by moving the coil around the inion until a phosphene that overlaps with the visual stimulus. For the anatomical reasons discussed above, V1 is likely to be affected when the phosphene is central and crosses the horizontal meridian.

The correspondence between the induction of moving phosphenes and the disruption of motion perception by stimulation of cortex in the region of human V5 was demonstrated by Stewart et al (1999). In their study V5 was located by a grid that contained 3 x 3 array of points, 1 cm apart, that was centered 3 cm dorsal and 5 cm lateral to the inion – coordinates that lie in the vicinity of V5 (Watson et al, 1993; Dumoulin et al, 2000). Each point of this grid was stimulated and subjects were asked to describe the induced percepts. In a subsequent experiment, the subjects adapted to a motion pattern and while viewing the aftereffect TMS was applied over the site from which moving phosphenes were most successfully induced; this stimulation reduced the duration of the perceived motion aftereffect, whereas stimulation of the posterior parietal cortex had no effect on its duration. The importance of this finding is that it offers a method for localizing the human motion area V5 when retinotopic maps for each subject are not available.

2.8.6. Neural basis of phosphenes

In addition to being a useful tool for determining the stimulation site, phosphenes can also be used to study the neural basis of visual awareness. As TMS can be used to directly activate a visual area that under visual stimulation is dependent on other cortical areas or the thalamic nuclei for input, this approach allows disentangling the information flow that is required to distribute activation throughout the cortex from the interactions that directly determine whether visual qualia are consciously perceived. A good example is the study by Cowey and Walsh (2000), who studied the neural basis visual perception by studying two blind subjects, with damage to optic nerve and V1, respectively. In both patients the lesion prevented information flow to the extrastriate cortex, but it was only the subject with V1 lesion who could not perceive phosphenes when TMS was applied over the intact extrastriate cortex. In this subject the lesion prevented not only information flow to extrastriate cortex, but also prevented this activation from reaching awareness. In contrast, when blindness was caused by damage to the optic tract, extrastriate activity could reach awareness. Pascual-Leone and Walsh (2001) subsequently demonstrated the importance of V1 for the perception of V5 phosphenes in normal subjects. They induced phosphenes from V5 and found that subthreshold TMS pulse, when applied over V1 5-45 ms after (but not before) the V5 stimulation, disrupted the perception of the V5 phosphene, implying that feedback from V5 to V1 is necessary for perception of moving phopshenes induced from V5.

Chapter 3: The role of V5/MT – V1 backprojections in awareness of visually presented moving stimuli

Introduction

The contribution of the striate cortex (V1) to visual awareness is a question that has raised much recent controversy. In some views V1 activity is not needed for awareness, this can simply arise as a result of activity in feature-specialized neurons in extrastriate cortex, with any integration of activation across visual areas being postconscious. In this view for example activity in movement-specialized extrastriate area V5/MT is necessary and sufficient for awareness or "microconsciousness" of visual motion (Zeki & Bartels, 1999). On other views V1 cannot participate in phenomenal vision because it is not directly connected with the frontal lobe (e.g. Crick & Koch, 1995).

By contrast however, the phenomenon of blindsight, namely, the manifestation of some visual processing despite the total loss of visual awareness caused by damage to V1 (e.g., Weiskrantz, 1986, 1997; Cowey & Stoerig, 1991) appears to suggest a role for V1 in awareness. There is also a growing body of literature which suggests that activity in V1 correlates with awareness: Super et al (2001), for example, have found that neurons in V1 are selectively suppressed when a monkey does not perceive a visual stimulus. Functional neuroimaging with human subjects revealed that activity in early visual cortex, and in particular V1, is predictive of whether or not a subject will perceive a stimulus (Ress & Heeger, 2003). Indeed, even in the absence of a visual stimulus, if a subject makes a false alarm response, activity in V1 resembles that seen on trials in which the subject was presented with and saw a stimulus.

There is ample evidence of backprojections from higher visual areas to V1 (Lamme et al., 2000; Bullier, 2001; Hupe et al., 2001; Hochstein & Ahissar, 2002). However, while several studies either show V1 to be important for awareness (e.g Cowey & Walsh,

2000; Ress & Heeger, 2003) or backprojections to be important for some aspects of visual perception (e.g. figure-ground segregation; Hupe et al., 2001; Angelucci et al., 2002; Heinen et al, 2005) it has not been demonstrated sufficiently that the recursive neural network between extrastriate and striate cortex is necessary for visual awareness. The studies mentioned above do not establish that it is the feedback and not the feedforward sweep of information that is the critical factor. An encouraging result was found in a transcranial magnetic stimulation (TMS) study in humans that showed that when TMS over V5/MT is delivered at intensities sufficient to induce perception of moving phosphenes, a subsequent TMS pulse (that is subthreshold for eliciting phosphenes) delivered over V1, 5 to 45 ms after V5/MT stimulation can degrade or remove the sensation of moving phosphenes (Pascual-Leone & Walsh, 2001).

Although this finding suggests that backprojections to V1 play a role in induced perception of moving phosphenes, it falls short of demonstrating a role for backprojections to V1 in normal visual awareness of real motion because no feedforward sweep was possible in the absence external visual stimuli as is the case when a real motion stimulus is present. What is required to establish the case of recurrent neural networks in visual awareness is a temporal dissociation between the contributions of extrastriate and striate cortex (see Pollen, 2003).

In the present study TMS was administered over V1 or V5/MT in different time windows during performance of a motion detection task in order to trace the flow of information that gives rise to awareness. Three accounts make different predictions about the location and timing of TMS effects over striate and extrastriate areas: According to the "microconsciousness" account (Zeki & Bartels, 1999) activity in any secondary visual area is sufficient to generate a conscious visual percept without requiring any feedback activity in V1. In motion detection this account has lead to suggestions that activation of V5/MT is sufficient for motion awareness (Barbur et al, 1993): once motion information has reached V5/MT, V1 is no longer necessary for motion detection. This view predicts that TMS over V1 should only lead to disruption

during feedforward activity and hence the critical time window of disruption by TMS over V5/MT should postdate that of disruptions caused by applying TMS over V1. It is possible that the activity between V1 and extrastriate cortex needs to be in synchrony for awareness to arise. The prediction from this synchronous activity theory is that the phenomenal experience of a particular attribute requires near-simultaneously experienced percepts in a number of cortical areas involved in the processing of that stimulus (Pollen, 1999). Thus TMS disruptions of motion detection should be effected by applying TMS over either V1 or V5 at similar times after stimulus onset.

If backprojections from V5/MT to V1 are necessary for motion awareness, however, TMS applied over V1 should disrupt motion detection at a later point in time than V5/MT stimulation, in addition to an earlier time window reflecting the role of V1 feedforward projections. As mentioned earlier one previous study suggested that TMS over V1 following TMS over V5 play a role in induced perception of moving phosphenes (Pascual-Leone & Walsh, 2001). However, the method of inducing moving phosphenes by TMS over V5/MT necessitated stimulation of V5/MT before V1, and thus precluded comparison of the critical time windows for activity in V1 and V5/MT in awareness of motion. Nor did it allow any clear conclusion about the role of backprojections to V1 in awareness of real, rather than induced phosphene, motion because of the possibility that interactions are different in the absence of a V1 input from the retina (Cowey & Walsh, 2000). Here, in three experiments, spatial localization, temporal specificity and the task specificity of TMS are controlled to test these three competing predictions and to probe the timing of interactions between human V5/MT and V1.

Experiment 1

The objective of Experiment 1 was to determine the role of V1 and V5/MT in motion detection once the feedforward sweep from V1 to V5 has been completed. This was done by applying TMS over either V1 or V5/MT at relatively late time windows

(chosen on the basis V1 latencies reported in the single-unit literature; Raiguel et al, 1989) at which the feedforward sweep is likely to have been completed.

Methods

Subjects. Seven participants (four males, mean age 23.4 years), five of whom were naïve to the objective of the study, took part in Experiment 1. The two other participants were naïve to the timing of stimulation in each TMS block. All experiments were undertaken with the understanding and written consent of each subject. Subjects were treated in accordance with the Declaration of Helsinki.

Stimuli. The stimuli were presented on a 19 inch (800 x 600 pixels) monitor. Viewing distance was 100 cm. Each trial began with a fixation point appearing in the middle of the screen for 500 ms. The motion stimulus consisted of 80 yellow dots (1 pixel each) placed at random positions within an imaginary square subtending .72 x .72 degrees of visual angle moving coherently either right or left on a black background (see Figure 3.2.). The displacement of the dots on motion trials was one pixel per frame. On "no motion" trials, the dots were stationary. Stimuli were presented for either 48 ms or 64 ms, with the motion stimulus consisting of either 3 or 4 frames lasting for 16 ms each. The speed of the motion stimulus was therefore 2.5 degrees/second.

Location of stimulation. TMS was administered with a Magstim Super Rapid stimulator (Magstim Company, UK). The coil was a 70 mm figure-eight coil, held with the handle pointing directly upwards. V1 and V5/MT were localised using a functional method in which the center of the coil is placed on the surface of the skull such that the stimulation elicits phosphenes that intrude on the center of the visual field, i.e., the target location (for a discussion of this method see Walsh & Pascual – Leone, 2003). For V1, the starting point of stimulation was 2 cm dorsal from the inion. The coil was then moved slightly to find a region from which the clearest phosphenes could be obtained, ending up in an average coil position for V1 stimulation 2.0 cm dorsal and 0.5 lateral from the inion. Initially, the intensity of stimulation was 70% of TMS output, and it was

increased if participants failed to perceive any phosphenes. It should be noted that although such occipital stimulation will clearly disrupt V1 it may have also affected areas close to V1, including V2. However, because perception of phosphenes is not possible without activity in V1 (Cowey & Walsh, 2000; Pascual-Leone & Walsh, 2001), and V1 is the likeliest site of stimulation (Kammer et al, 2001), it is parsimonious to attribute the effects in our study to V1 stimulation (see also Campana et al, 2002).

For V5/MT, the starting location for stimulation was 2 cm dorsal and 4 cm lateral from the inion. The coil was then moved slightly to find a region from which moving phosphenes could be induced (the reliability of this method in locating V5/MT has been demonstrated by Stewart et al, 1999) giving an average coil position of 3.1 cm dorsal and 5.1 cm lateral from the inion. V5/MT in the left hemisphere was stimulated in all participants because it has consistently been found to produce phosphenes more reliably than the right hemisphere (Stewart et al, 1999; Beckers & Hömberg, 1992; Antal et al, 2001). Due to the size of the cortical surface area covered by the figure-of-eight coil, it is likely that the satellites of V5/MT (e.g., MST) are also affected by this stimulation (see figure 3.1. for stimulation sites). For the experimental blocks in both experiments, the intensity of TMS was decreased to 60 % at which none of the participants reported phosphenes during the experimental blocks.

Stimulation Onsets. There were six TMS conditions with double pulse TMS applied at either 60 and 80 ms; 80 and 100 ms; or 100 and 120 ms from stimulus offset over V1 or V5/MT (124 and 144 ms; 144 and 164 ms; or 164 and 184 ms from stimulus onset for five participants, 108 and 128 ms; 128 and 148 ms; and 148 and 168 ms for two participants). Double pulses of TMS were applied in order to make use of the summation properties of TMS pulses – double pulse TMS gives larger effects than single pulse TMS (as one would expect) but still allows good temporal resolution defined by the temporal

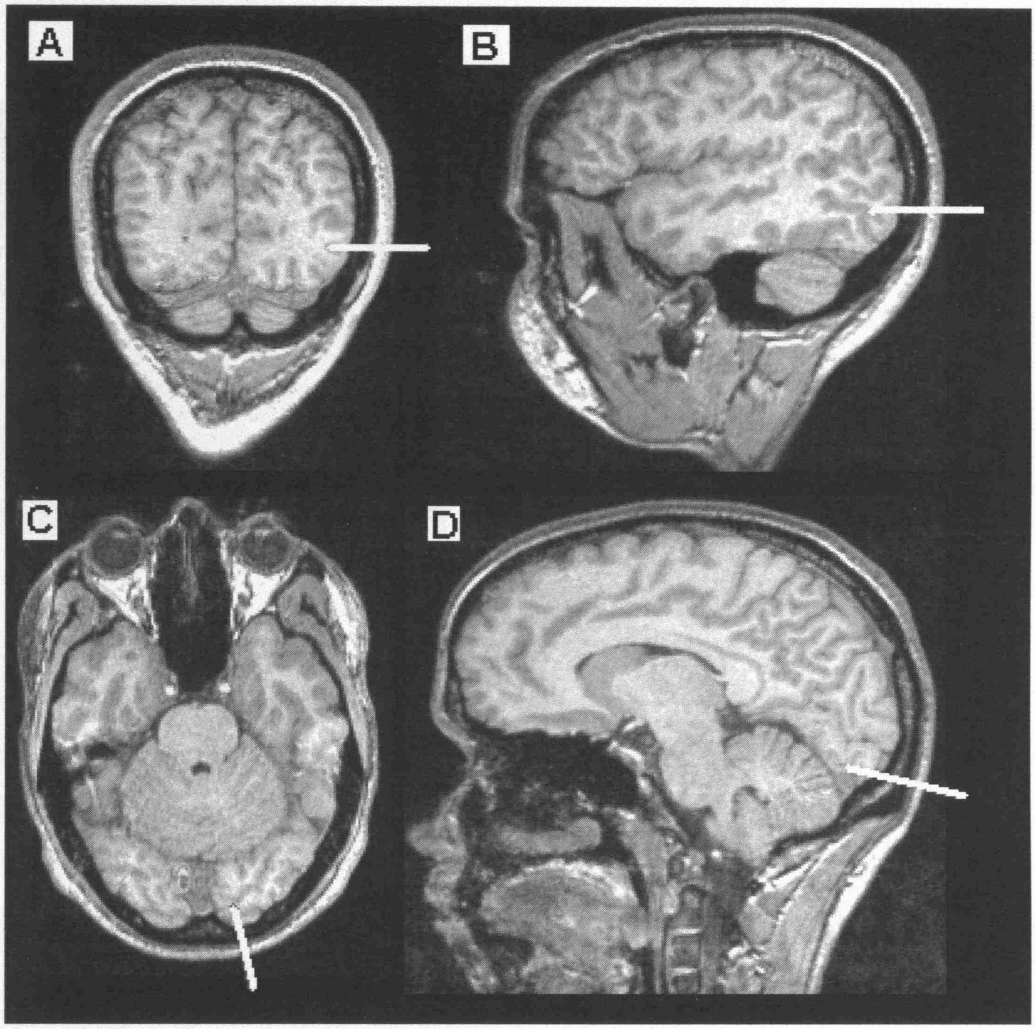


Figure 3.1. *Coil locations of V5/MT (A: transverse view; B: sagittal view) and V1 (C: transverse view; D: sagittal view) stimulation on MRI image of one participant. The white lines represent the TMS trajectory. Note that left and right are reversed.*

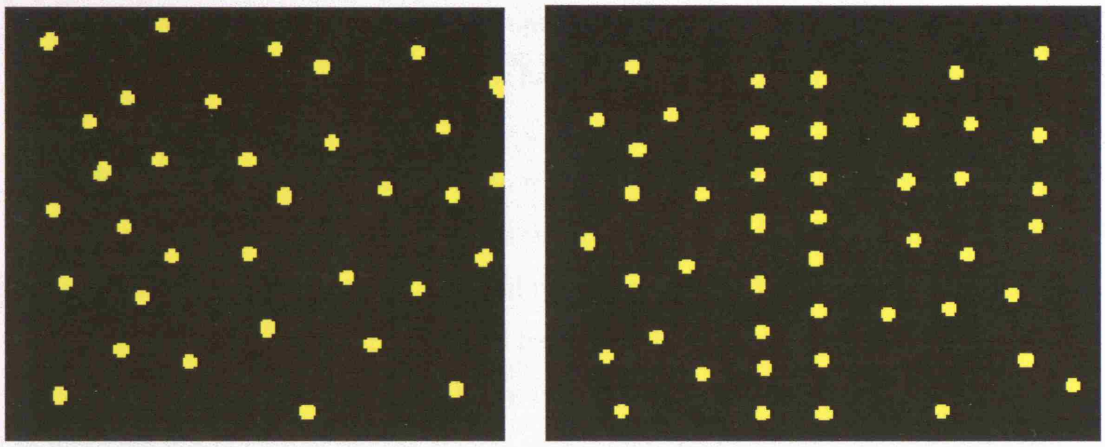


Figure 3.2. *Stimuli used in Experiments 1, 2 and 3. On the left, an example of motion stimulus used in Experiments 1 and 3. On motion present trials, all dots moved either to the left or to the right. On motion absent trials, all dots were stationary. On the right, an example of the stationary stimulus in the "present" trials used in Experiment 2. The figure shows a path-like pattern amongst randomly distributed dots. On absent trials, all dots were distributed randomly. Both stimuli consisted of 80 dots.*

distance between the two pulses (see Walsh & Pascual-Leone, 2003). These stimulation onsets are consistent with experiments that have used TMS to address the timing of V5/MT activity in tasks involving moving random-dot patterns. For instance, Hotson and Anand (1998) and Anand et al (1999) disrupted direction discrimination of a moving random-dot pattern by administering single-pulse TMS over V5/MT between 100 – 175 ms from stimulus onset. Disruption of motion speed judgments as a result of V1 stimulation within this time window has also been observed (Matthews et al, 2001).

Procedure. The participants' task was to report whether or not they detected motion in the display. Each of the TMS conditions was run in one block of 75 trials each, 50 were motion trials (25 left movement, 25 right movement) and 25 no motion trials. There were more motion trials than no motion trials in order to maximise the behavioural effects of TMS (as TMS has been shown to disrupt motion perception by making moving stimuli to stop or appear slower, rather than inducing false alarms with static stimuli (e.g., Matthews et al, 2001)). All types of trials were intermixed randomly within a block. The order of blocks was counterbalanced across subjects. Two baseline conditions with no TMS were also run, one before and one after the TMS blocks. In order to obtain a stable level of performance, two practice blocks preceded the experiment. If performance in these blocks exceeded a d' value of 2.5, the task was made more difficult by removing one frame from the stimulus. If performance was below a d' value of 1, the task was made easier by adding a frame. Five participants performed the motion task with four frames (stimulus duration 64 ms), two with three (48 ms).

Data Analysis: Signal detection theory.

Signal detection theory is based on three assumptions. Firstly, that the evidence extracted by the obsever about the signal can be represented by a single number; secondly, this evidence is subject to random variation, and thirdly, observer's choice is made by applying a simple criterion to the evidence (Wickens, 2001). An assumption of

SDT is that noise is normally distributed. When a signal is presented on top of noise, the amount of sensory activity is shifted to the right (i.e. it is increased) by an amount equal to that sensory systems sensitivity to that signal. Subject's sensitivity (d', measured in z-score units, i.e. standard deviation units) refers to the difference between the mean amount of sensory activity generated by the noise alone trials and the signal+noise trials (Wickens, 2001). The central aspect in calculating subject's sensitivity (d') in s ignal detection theory is therefore the ratio of hits and false alarms ($d' = Z_{\text{False alarms}} - Z_{\text{Hits}}$).

Results

This experiment showed that V5/MT has an early critical time window for motion detection followed by a later critical time window for V1. Figure 3.3. shows motion detection performance (d') as a function of the TMS condition averaged across the seven participants. A within-subjects ANOVA indicated a significant interaction between site and time ($F(2,12) = 10.805$, $p = 0.0001$; MSE= 0.115). Sidak-adjusted paired-sample t-tests revealed that V5/MT stimulation at the first (60-80 ms) time window produced a significant disruption in motion detection by comparison with no TMS condition ($t(6) = 7.821$; $p = 0.001$; SEM = 0.095), and by comparison with the second (80-100 ms) time window ($t(6) = 6.231$; $p = 0.002$; SEM = 0.116) and the third (100-120 ms) time window ($t(6) = 4.557$; $p = 0.012$; SEM = 0.147). As can be seen in Figure 3.3., the effect of V5/MT stimulation on motion detection did not differ from the no TMS condition at the second or the third time window.

In contrast, V1 stimulation produced a disruption in motion detection at the second (80-100 ms) time window relative to no TMS condition ($t(6) = 3.952$; $p = 0.022$; SEM= 0.178) and to the first (60-80 ms) time window ($t(6) = 4.921$; $p = 0.008$; SEM= 0.141), and third time window (100-120 ms, $t(6) = 1.3.651$; $p = 0.032$; SEM= 0.286). As can be seen in Figure 3.3, V1 TMS did not disrupt motion detection performance at the first (60-80 ms) or the third (100-120 ms) time windows in comparison to the no TMS condition. At the critical time windows the effect of V5/MT stimulation (in the first

time window) and V1 stimulation (in the second time window) were comparable (t(6) = 0.265; p = 0.800; SEM= 0.153).

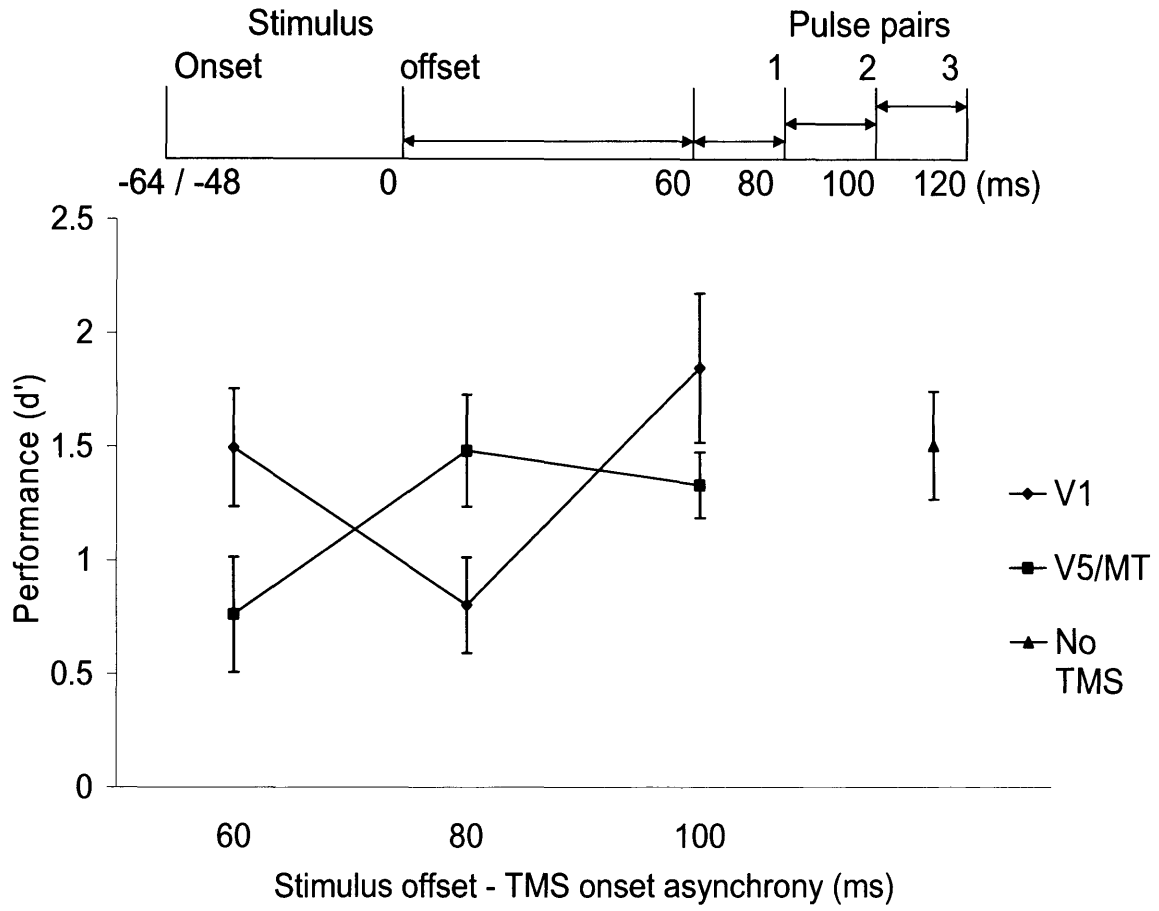


Figure 3.3. *Timeline of an experimental trial and the mean performance (d') of the 7 subjects at each stimulus offset - TMS onset asynchrony in the motion detection task. Each trial began with a 500 ms fixation point, which was followed by the test stimulus with duration of either 48 or 64 ms, depending on the participant's ability. TMS was applied after the offset of the stimulus at intervals indicated in the method.Error bars indicate +/- 1 SEM.*

Experiment 2

The pattern of results in Experiment 1 suggests that backprojections from V5/MT to V1 play a role in awareness of real motion. However, an alternative explanation of these results is that TMS disrupted awareness in general, rather than motion specifically. TMS can have the effect of degrading the visibility of stimuli of short durations (Amassian et al., 1989; Kammer & Nusseck, 1997). It is therefore possible that at the critical time windows TMS made the dots (both moving and stationary) less visible. To directly examine whether the TMS effects in Experiment 1 are selective to motion, Experiment 2 involved the detection of a stationary pattern that was constructed from dots of same size and contrast as in Experiment 1.

Methods

Subjects. Seven participants (four males and three females, mean age 23.8 years) took part in Experiments 2, six of whom had participated in Experiment 1.

Stimulus. The stimulus consisted of two vertical columns of six dots (1 pixel each) each, extending 0.72 degrees of visual angle vertically, separated by a distance of five pixels. This path-like pattern appeared at one of four possible horizontal locations within the same imaginary square as that used in Experiment 1 (see Figure 3.2.). Sixty-eight noise dots were distributed randomly in the other positions of the imaginary square to complete the number of dots to 80 (as in Experiment 1). On "absent" trials all dots were distributed randomly. The stimuli were presented for either 48 ms or 64 ms. For the six participants who had taken part in Experiment 1, stimulus duration was same as in that experiment. For the subject who had not taken part in Experiment 1, the stimulus duration was 64 ms. In all other aspects the stimulus and viewing conditions were identical to that of Experiment 1.

Location and onsets of stimulation. For the six participants who took part in Experiment, V1 and V5/MT coordinates that were determined in Experiment 1 were used. For the additional participant the localization was carried out using the procedure described in Experiment 1 (see Figure 3.1.). Stimulation was carried out as described in Experiment 1. TMS onsets were identical to those in Experiment 1.

Procedure. The participants' task was to report whether or not they detected the presence of the path-like pattern. Each TMS condition was run in one block of 60 trials (40 "present" trials and 20 no motion trials intermixed randomly). The order of blocks was counterbalanced across subjects. Two baseline conditions with no TMS were also run, one before and one after the TMS blocks. In order to obtain a stable level of performance, two practice blocks preceded the experiment. If performance in these blocks exceeded a d' value of 2.5, the task was made more difficult by adding 10 noise dots to the display. If performance was below a d' value of 1, the task was made easier by decreasing the number of noise dots by ten.

Results

Figure 3.4. shows pattern detection performance (d') as a function of the TMS condition averaged across the seven participants. As can be seen in Figure 3.4., there was no effect of TMS on the detection task. This was confirmed by a within subjects ANOVA which showed no interaction between stimulation site and time window ($F(3,18) = 0.258$; $p = 0.902$; $MSE = 0.106$) and no main effects of stimulation site ($F(1,6) = 0.327$; $p = 0.727$; $MSE = 0.161$) and stimulation onset ($F(3,18) = 0.300$; $p = 0.746$; $MSE = 0.121$). These results rule out any non-specific accounts for the TMS effects on motion detection (e.g. in terms of general effects of masking, or a failure to detect the dots). In addition, subjects' phosphene sensitivity was tested when stimulated in darkness at the intensity (60%) and frequency (double pulse) used in the experiment, and when they were looking for phosphenes rather than the visual stimulus. For four of the seven participants of Experiment 1 (three of whom also took part in Experiment 2), this

stimulation was subthreshold for eliciting phosphenes. The three participants who did report an occasional appearance of phosphenes on some trials took part both in Experiment 1 and 2. Thus, as all participants displayed the same temporal relationship of V5/MT and V1 activity, the pattern of results obtained here cannot be explained in terms of masking by phosphenes. It is important to note that phosphenes are only perceived reliably when subjects are looking for them. Stimulation above phosphene threshold while subjects are performing a visual task does not usually induce phosphene perception.

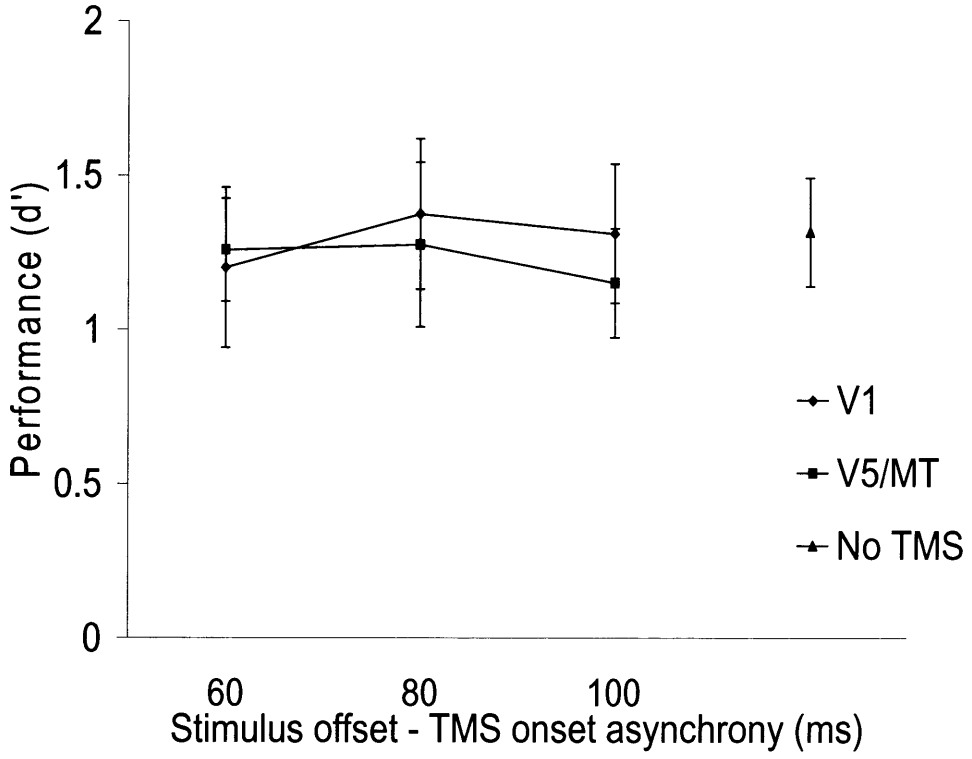


Figure 3.4. *The mean performance (d') of the 7 subjects at each stimulus offset - TMS onset asynchrony in Experiment 2. The effective time window for interference with motion stimuli has no effect on the detection of stationary pattern stimuli.Error bars indicate +/- 1 SEM.*

Experiment 3

The stimulation time windows in Experiment 1 were chosen to reveal feedback connections from V5/MT to V1 that are likely to occur relatively late in processing. In order to determine whether backprojections from V5/MT to V1 play a role in awareness of motion stimuli in the presence of V1 feedforward activity, the objective of Experiment 3 was to investigate whether the motion task used in Experiment 1 is dependent on the feedforward projections from V1 to V5/MT. As V5/MT stimulation disrupted motion detection at the 60-80 ms time window, stimulation of V1 at the immediately preceding time window (40-60 ms) should impair motion detection by disrupting the feedforward projections from V1 to V5/MT. Secondly, to confirm the specificity of the time windows of Experiment 1, V1 and V5/MT were also stimulated at three time windows that postdate the time windows of Experiment 1.

Methods

Subjects. Seven participants (three males and four females, mean age 25.2 years), four of whom had taken part in Experiments 1 and 2, took part in Experiment 3.

Stimulus. The stimulus was identical to that in Experiment 1. For the four participants who had taken part in Experiments 1 and 2, stimulus duration was kept constant.

Stimulation location and onsets. V1 and V5/MT were localized using the technique described in Experiment 1. For the four participants who had taken part in Experiment 1, coordinates from Experiment 1 were used. Double pulses of TMS were applied over V1 or V5/MT at four different time windows: 40 and 60 ms; 120 and 140 ms; 140 and 160ms; and 160 and 180 ms from stimulus offset. Other aspects of stimulation were carried out as described in Experiment 1. The order of sessions was counterbalanced across participants.

Procedure. The experiment was run in two sessions, the order of which was counterbalanced across participants. One session consisted of the 40-60 ms TMS condition and the no TMS condition, the second consisted of the three late TMS time windows (120 -140 ms; 140-160 ms; 160-180 ms) and the no TMS condition. In each session the no TMS condition was run in two blocks, one before and one after the TMS blocks. In all other aspects the procedure was identical to that in Experiment 1.

Results

This experiment showed that an early V1 time window, consistent with feedforward activity, is critical for awareness of visual motion (see Figure 3.5.). At the 40 – 60 ms stimulation time window a within-subjects ANOVA indicated a significant effect ($F(1,6) = 15.993$; $p = 0.0001$; MSE= 0.007). Sidak-adjusted paired-sample t-tests were carried out (In Sidak-adjusted analysis, the experimentwise error is corrected by $\text{alpha}_{ew} = 1 - (1 - \text{alpha}_{pw})^{1/p}$ where ew=experimentwise, pw=procedurewise, and p = number of procedural tests (Kirk,1982)). These revealed that V1 stimulation at this time window produced a disruption in motion detection (M d' = 1.4) in comparison to the No TMS condition (M d'= 2.0), $t(6) = 4.701$; $p = 0.01$; SEM= 0.133, and the V5/MT condition (M d' = 2.2), $t(6) = 4.971$; $p = 0.008$; SEM= 0.157; whereas the V5/MT condition did not significantly differ from the No TMS condition ($t(6) = 1.033$; $p = 0.715$; SEM= 0.147). This V1 effect at the 40-60 ms time window is likely to reflect a disruption to feedforward activity in V1, as it occurs immediately before the V5/MT critical time period in Experiment 1 (at 60 – 80 ms), and V1 is the major source of V5/MT input (Maunsell & Van Essen, 1983a,b).

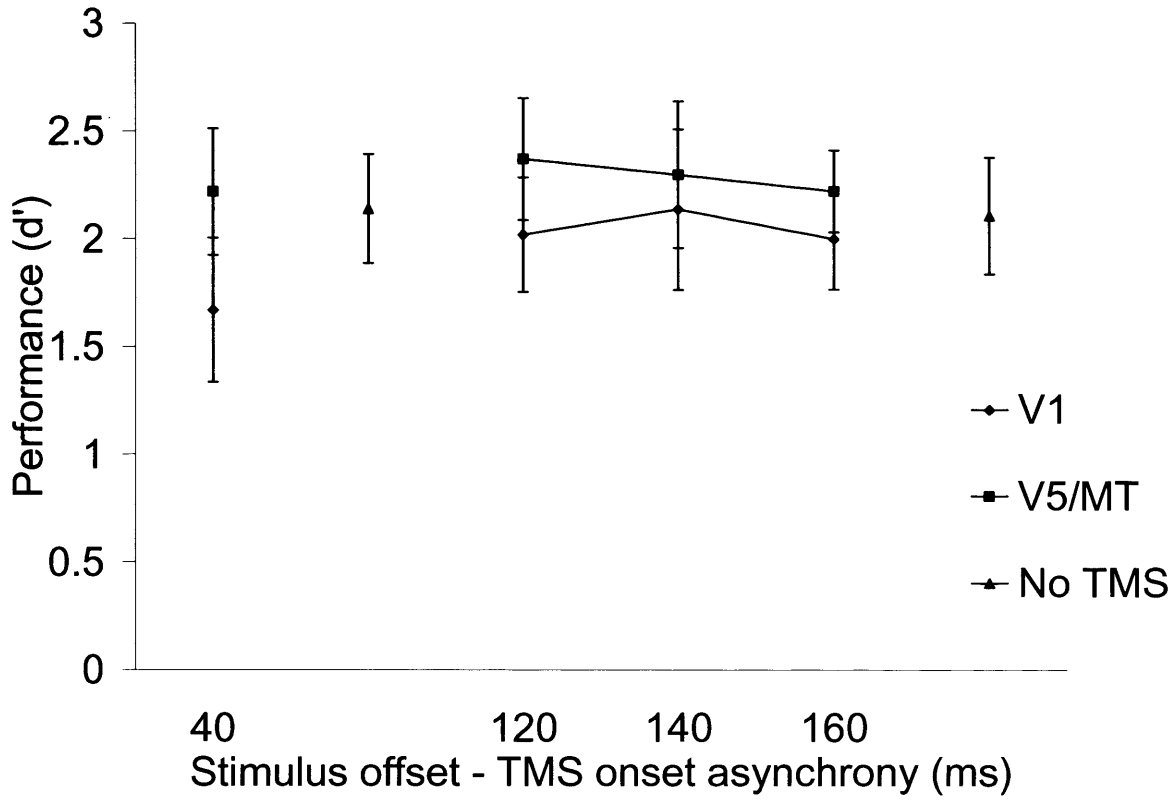


Figure 3.5. *The mean performance (d') of the seven subjects at each stimulus offset – TMS onset asynchrony in Experiment 3. As the "early" (40-60 ms) and "late" (120 – 140, 140 -160 and 160 – 180 ms) TMS conditions were run in separate sessions, subjects' performance in the No TMS condition are presented separately. The "early" V1 time window is critical for awareness of visual motion. Error bars indicate +/- 1 SEM.*

Late time windows were run in a separate session. Mean d' for the No TMS condition in this session was 2.2. Mean d' values for V1 TMS were: 2.0 for 120-140 ms onset, 2.1 for 140- 160 ms onset, and 2.0 for 160 – 180 ms onset; for V5/MT TMS mean d' values were: 2.4 for 120-140 ms onset, 2.3 for 140-160 ms onset, 2.2 for 160 – 180 ms onset. A within-subject ANOVA indicated an absence of a site by stimulation onset interaction ($F(3,18) = 0.613$; $p = 0.657$; MSE= 0.143), as well as an absence of main effects of site ($F(1,6) = 1.420$; $p = 0.280$; MSE= 0.491) and stimulation onset ($F(3,18) = 1.523$; $p = 0.257$; MSE= 0.153).

A paired-sample t-test showed that the two No TMS conditions in Experiment 3 did not significantly differ from each other ($t(6) = 0.301$; $p = 0.774$).

Discussion

The present results show two critical periods of V1 activity, one preceding (at 40 - 60 ms from stimulus offset) the V5/MT critical period (that occurred at 60- 80 ms from stimulus offset) and another postdating (at 80 – 100 ms from stimulus offset) the V5/MT critical period. Importantly, stimulation of V5/MT at the critical periods of V1 or of V1 at the critical period of V5/MT had no effect on participants' performance. This double dissociation of critical periods suggests that although V5/MT obtains visual information through V1 feedforward activity (reflected in the early V1 critical period predating that of V5/MT), backprojections from V5/MT to V1 remain critical for awareness of motion, as demonstrated by the presence of the late V1 critical period postdating that of V5/MT.

The lack of V5/MT effect at 80 – 100 ms or at any of the later time periods is important in indicating that once V1 has received the backprojections, activity in V5/MT is no longer necessary for motion awareness (see Figure 2), and that the late V1 effect cannot be attributed to another cycle of feedforward activity (as this would imply the presence of a further V5/MT critical period). This double dissociation between the critical time

windows of V5/MT and the late period of V1 activity in motion detection demonstrates the importance of backprojections in normal vision and shows that the role of V1 extends beyond the feedforward sweep.

In contrast, TMS applied over V1 and V5/MT at the same time windows did not disrupt subjects' performance in the shape detection task, implying that the effects of TMS on motion detection were not due to a disruption in subjects' ability to perceive the dots of which the visual stimuli consisted. Rather, it was awareness of motion that was selectively disrupted. However this is not to say that V1 is not necessary for perception of attributes other than motion; in fact stimulation of V1/V2 has been shown to abolish conscious perception of stationary visual stimuli, but only of very short durations and low contrast, whereas the stimuli used in the present experiment were of high contrast. It is also possible that V1's critical time window in perception of static stimuli postdates the stimulation time windows used in Experiment 2.

These results clearly demonstrate that integrity of the early V1 feedforward activity does not obviate the need for the late V1 activity. Moreover, stimulation of V1 during this later phase of activity is not only capable of disrupting the sensation of phosphenes (as previously reported in Pascual-Leone & Walsh, 2001) but also can impair detection of a real motion stimulus, to the same degree as V5/MT stimulation, as assessed psychophysically in the present experiment. These are the first findings to show that V1 activity at a later period than V5/MT's activity is necessary for detection of *real* motion in humans.

These findings are inconsistent with the view that activity in an extrastriate area selective for a particular attribute is sufficient for awareness of that attribute (Zeki & Bartels, 1999). They also argue against the possibility that perceiving a visual stimulus requires simultaneous activity in all visual areas involved in processing of that stimulus (see Pollen, 1999; 2003) – although whether synchronous activity is more important when more than one attribute is present, i.e. in binding for example when being aware of the colour and movement of a stimulus, is still a good question to be examined.

A number of theoretical frameworks have made a distinction between feedforward and feedback activity in the visual system and, consistent with my findings, it has been suggested that these two processes reflect a qualitative difference between unconscious and conscious vision (Lamme, 2001). Other theories have emphasized the role that feedback activity plays in computing local details in images that cannot be computed by the large receptive fields of extrastriate neurons (Bullier, 2001; Hochstein & Ahissar, 2002). In these models, awareness of global representations of the visual field, provided by extrastriate areas precedes awareness of local details computed in V1. The present findings are not inconsistent with these theories, as the experimental task may have required computation of local details in V1 as the motion was across very short distances (each dot moved only one pixel between the frames), and it could be argued that the need for fine spatial detail necessitated the recruitment of small receptive fields of V1. The finding that large phosphenes induced by V5 TMS with motion components spanning almost a whole hemifield can be disrupted by a subsequent subthreshold V1 TMS pulse does argue against the possibility that only the perception of "local" motion is dependent on V5-V1 backprojections. However contrary to phosphene perception, awareness of the motion stimulus in the present study required not only the encoding motion but also of fine spatial details of the dots that were moving (as each dot had a size of only 1 pixel) and this might have amplified the need for V5-V1 backprojections. Studies that manipulate multiple stimulus features within one experiment are needed to resolve this issue.

Chapter 4: Activation level of V1 determines the awareness of activation of V5/MT

Introduction

Of the many visual stimuli that impinge on the retina, few are consciously perceived at any one time. Despite simultaneous activity in visual areas responding to colour, motion, texture or shape and despite evoked visual responses to stimuli in all parts of the visual field, at any one time we are aware of only a few details in a restricted part of the visual field. It has been suggested that awareness of visual stimulus attributes requires only activity in the appropriate extrastriate area (Zeki & Bartels, 1999)' for instance, awareness of motion will only require activity in V5/MT. However, selective damage to any one extrastriate area does not abolish awareness of any single attribute; it merely raises thresholds for detection and discrimination of the attributes for which it is selective. For instance, a lesion of V4/V8 elevates thresholds for colour judgements (Heywood & Cowey, 1987) and a lesion to V5/MT does lead to permanent deficits in motion detection and speed discrimination, but the deficits are moderate (Schiller, 1993). Furthermore, Newsome and Pare (1988) reported strong transient impairment of direction discrimination, but the degree of recovery was substantial, the permanent deficit in threshold being only a few percent.. This suggests that these extrastriate areas are part of a larger network that can in their absence still function under certain conditions. By contrast damage to V1 in humans (Weiskrantz et al, 1974) and monkeys (Cowey & Stoerig, 1995) can abolish visual awareness of all stimulus attributes in the corresponding parts of the visual field.

Several other lines of evidence have also identified V1 as the area which is most likely to play a central role in awareness. Firstly, it is reciprocally connected with more visual areas than any other cortical region, and it is in the heart of both the magno- and parvocellular processing streams, making it from an anatomical point of view a strong candidate to play a central role in visual perception (Felleman & Van Essen, 1991).

That V1's role in visual perception extends beyond providing input to areas that are traditionally believed to be higher in the visual hierarchy, is suggested by the existence of prominent feedback connections from extrastriate areas to V1 (Felleman & Van Essen, 1991). These feedback connections from areas such as V2, V3 and V5/MT are arranged in topographic fashion, and their periodicity matches the periodic distribution of specific functional properties in V1 (Angelucci et al, 2002; Salin et al, 1995). These qualities allow V1 to sample information about various attributes that are encoded by different regions in the extrastriate cortex.

The importance of backprojections from V5/MT to V1 in conscious perception of moving phosphenes was demonstrated by Pascual-Leone and Walsh (2001), who showed that a subthreshold pulse applied of V1 5 to 45 ms after a phosphene has been induced by TMS over V5/MT, disrupts the perception of that phosphene. That such backprojections are also important in conscious perception of real motion stimuli with an intact V1- V5/MT feedforward sweep was shown in experiments described in Chapter 3. However, these studies have only shown that awareness of motion can be impaired by disrupting V1 at a later time point that V5/MT, and while the use of this "negative" approach of inducing disruptions is often useful in TMS research, in this case it cannot establish whether it is the recursive inputs from extrastriate cortex that determine the content and presence of awareness. Furthermore, it has never been shown that the attributes of awareness are dictated by these backprojections, yet it is a cornerstone of many current views of visual awareness (Lamme, 2001; Hochstein & Ahissar, 2002; Pollen, 1999, 2003). It is therefore essential to determine how the V5-V1 backprojections create awareness of motion, and this requires the use of a "positive" approach that attempts to create rather than to abolish awareness by facilitating these backprojections.

The possibility addressed in the present chapter is that it is the level of activation in V1 that determines whether V5/MT activation reaches awareness. An fMRI study has recently found that the activation level in V1 correlates more with subjects' percept rather than with the actual physical attributes of the visual stimulus; that is, the strength

of the BOLD signal in V1 was high when subject reports the presence of a stimulus, even when the target had not been presented, and it was low when the subject reports the absence of the stimulus, even when the target has been presented (Ress & Heeger, 2002). However as imaging studies show correlation and not causality, it is not clear whether the activation level in V1 *determined* the presence of the conscious percept. It therefore needs to be determined whether V1 activity is causal to the conscious perception of activation in extrastriate areas. It is possible that high level of activation in both of V5/MT and V1 is prerequisite for awareness of motion – this is close to, but not identical, to Pollen's (1999) suggestion that awareness of an attribute requires simultaneous activation in all visual areas that are involved in its processing. Alternatively, it might be solely the activation level of V1 that determines whether a conscious percept motion can arise; in this view even low levels of activation in V5/MT can reach awareness if activation level of V1 is high enough. Other neuroscientific theories that have proposed a critical role for extrastriate – V1 interactions in visual awareness do not make specific hypotheses on how extrastriate activation reaches awareness via V1. In Lamme's (2003) view, recurrent interactions between extrastriate and striate cortex are necessary for binding and segregation of visual information that results in perceptual organisation, enabling phenomenal awareness, but how this is reflected in activation levels throughout the visual cortex is unclear.

Whereas TMS applied over V1 above phosphene threshold induces the experience of a small, stationary phosphene located in the contralateral lower visual field, suprathreshold TMS over V5/MT elicits a phosphene also in the contralateral visual field, but as one would expect given the differences between V1 and V5/MT receptive field properties, the V5/MT phosphene is much bigger than the V1 phopshene, and in 60-80 percent of subjects it appears moving (Kammer et al, 1999; Stewart et al 1999; Pascual-Leone & Walsh, 2001; Walsh & Pascual-Leone, 2003).The fact that phosphenes reflect the properties of the underlying cortex enables one to determine the conditions in which activation of a specific visual area reaches conscious awareness. This experiment investigated, by manipulating the induced activation level of V1 using TMS, whether it is the level of activity in V1 that dictates whether subjects' consciously

perceive activation originating in V5/MT, or whether V5/MT - V1 cortical backprojections determine the content of conscious awareness.

Methods

Subjects Eight subjects (five males, three females, mean age 25.3 years) participated in the experiment, six of whom were fully naïve to its purpose. Two of the subjects that were not were still naïve to the timing of the pulses. Experienced subjects were used because the variability in phosphene threshold is lower in such subjects.

Localisation of stimulation sites. TMS was administered with two Magstim Super Rapid stimulators (Magstim Company, UK). The pulses were triggered remotely using a computer that controlled both stimulators. 50 mm figure-of-eight coils were used. For six of the subjects, the scalp coordinates of V5/MT were obtained by inducing selective deficits in motion detection when TMS was applied over a location that corresponded with the anatomical delineation of V5/MT by structural MRI in each subject. Four of these six subjects also perceived moving phosphenes when this site was stimulated; the other two perceived large, often twinkling but stationary phosphenes. For the other two subjects, V5/MT was localised by finding a site from which moving phosphenes were most reliably induced. The mean location of V5/MT defined in this way was 3.1cm dorsal and 5.4 cm lateral (left) from the inion. Six of the eight subjects perceived moving phosphenes with V5 stimulation. V1 was localised by determining the coordinates of the scalp overlying the calcarine sulcus from subjects' MRI images. If stimulation of this site did not induce clear phosphenes that shared the retinotopic spatial location of the V5 phosphene, the coil was slightly moved until co-registration was obtained. Coil orientation for V5 stimulation was such that the handle pointed upwards, at an angle of approximately 45 degrees counterclockwise. The average coil position for V1 stimulation was 1.9 cm dorsal and 0.4 cm lateral (left) from the inion. The left hemisphere was stimulated in all participants because it has consistently been found to produce phosphenes more reliably than the right hemisphere (Stewart et al, 1999). For V1 stimulation the coil handle was pointing downwards, at an angle of approximately 120 degrees clockwise. Coil orientation was constant for each subject.

Stimulation parameters.

In all experiments, phosphene thresholds were determined using a modified binary search paradigm (Tyrrell & Owens, 1988). In Experiment 1, V1 was stimulated at a suprathreshold intensity that was always 3-4% above threshold to ensure that subjects reported a phosphene on every trial, and V5/MT was stimulated 20% below phosphene threshold. In a further condition, both sites were stimulated 20% below phosphene threshold in the six subjects who perceived moving phosphenes with V5/MT stimulation.

Procedure

Subjects' eyes were covered throughout the experiment. All subjects reported phosphenes that were restricted to the visual field contralateral to stimulation. At these relatively low stimulation intensities it is less likely that either satellite regions of V5/MT containing bilateral receptive fields or V5/MT in the opposite hemisphere are excited; therefore subjects tend to perceive only a unilateral phosphene (as they did in the current study). Higher levels of stimulation than those used here may elicit phosphenes that cross the midline, indeed higher levels of repetitive V5/MT stimulation during a motion perception task were found to disrupt motion perception in both hemifields in previous studies (Hotson et al, 1994; Walsh et al, 1998). The mean phosphene thresholds for V5 and V1 with the coil orientations used were respectively 72 % and 69 % of maximum output of the stimulator.

Initially, a pilot study (three subjects) was conducted in which subjects were asked to freely describe and draw their percepts, if any. In the main experiment, subjects were additionally asked to rate their percept using the size/shape scale that was constructed on the basis of subjects' responses. Specifically, subjects were asked to judge whether their size and shape of their percept was like a (1) V1 phosphene; (2) mixture of V1 and V5 phosphenes; (3) V5 phosphene; subjects responded (0) when phosphene was absent.

Subjects were asked to describe their perception of motion using the scale described by Pascual-Leone and Walsh (2001) motion scale (0 = phosphene was absent; 1 =

phosphene was stationary; 2 = uncertain whether phosphene was moving or stationary; 3 = the phosphene was moving). Furthermore, subjects were also asked to draw their phosphenes if they differed from the phosphenes induced by TMS applied over V1 only. In the reported experiment TMS pulses were delivered with a V5 to V1 stimulation asynchrony between -80 ms (that is, V1 before V5) and +80 ms (V5 before V1). For each SOA condition, six pulse pairs were administered. For three of these pulse pairs, the V5/MT coil was lifted off the surface of the skull by 2 cm, so that V1 only was stimulated. These three V1 only- trials either preceded or followed the dual stimulation- trials.

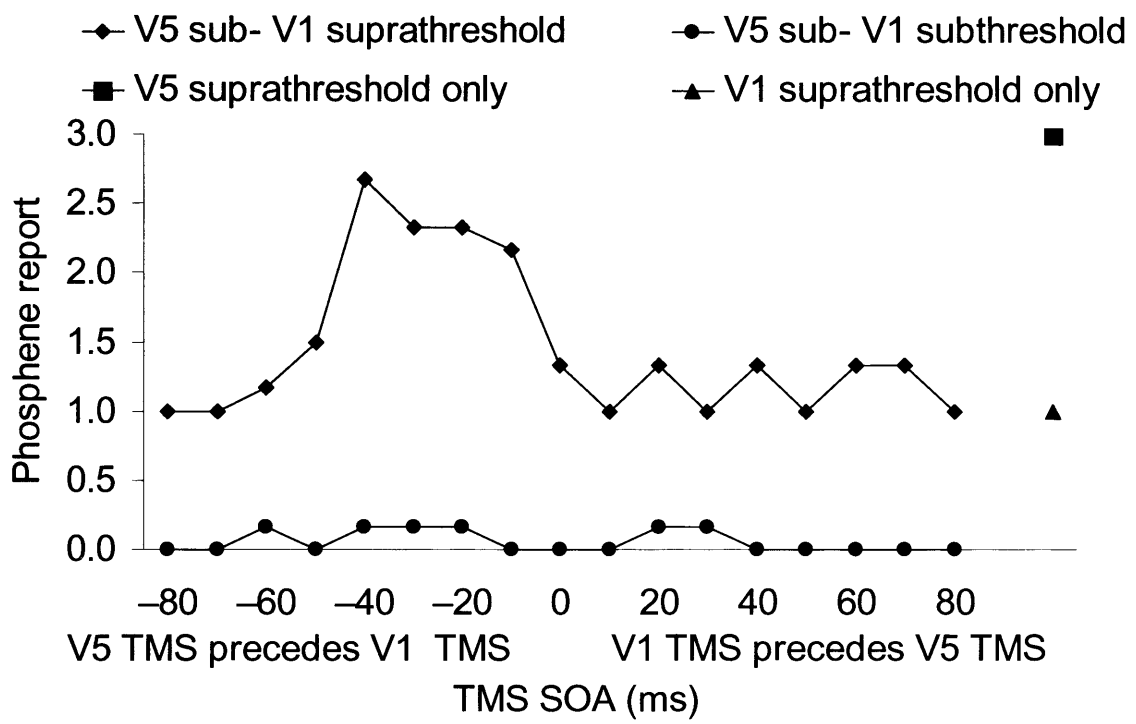
The order of SOAs was intermixed pseudo-randomly. The order of stimulation was reversed in consecutive conditions (so that a condition in which V1 preceded V5/MT TMS by a given SOA was followed by a condition in which V5/MT precedes V1 by the same SOA). Whether a given timing started with a "V5/MT before V1" condition or vice versa was counterbalanced. Subjects were asked to compare the phosphenes induced by TMS solely over V1 to the phosphenes induced by the paired pulses. Trials on which a TMS pulse was applied only over V5/MT were dispersed randomly throughout the experiment. This stimulation never induced phosphenes.

Results

Figures 4.1 and 4.2 show subjects' phosphene reports as a function of the V5/MT – V1 TMS stimulation asynchrony. When TMS was applied unilaterally to V1 above phosphene threshold, subjects reported, as expected, the presence of a small, stationary phosphene located in the contralateral lower visual field within a few degrees of the vertical meridian. Suprathreshold TMS over V5/MT elicited the experience of a phosphene, also in the visual field contralateral to simulation, that was moving (see Figure 4.1.), larger and of a different shape from the V1 phosphene (see Figure 4.2.). At most SOAs, subjects merely perceived their normal V1 phosphene; that is, the V5 subthrehsold stimulation had no influence on their percept. Critically, however, when a sub-threshold pulse was applied over V5/MT and was followed, 10-40 msecs later, by a

suprathreshold pulse over V1 subjects reported a phosphene that was not merely the suprathreshold V1 phosphene. Rather, it acquired features of a suprathreshold V5 phosphene: subjects now reported the perception of movement (see Figure 4.1.); when TMS was applied over V5/MT at subthreshold level 40 ms before V1 was stimulated at suprathreshold level, five of the six subjects (who perceived moving phosphene when V5 was stimulated at suprathreshold level by itself) reported the perception of moving phosphenes. In contrast, V1 suprathreshold stimulation by itself always induced stationary phosphenes in all subjects.. Furthermore, the shape and size of their percept was now a mixture of V1 and V5/MT phosphenes (see Figure 4.2.); five of the eight subjects perceived a mixture of V1 and V5/MT phosphenes when TMS was applied over V5 30 ms before V1.

In contrast, when sub-threshold TMS (i.e. producing no phosphene on its own) was applied over V5/MT and V1, subjects did not consistently report phosphenes at any of the SOAs (see Figure 4.1.); only one subject occasionally reported the perception of a stationary phosphene.


V5 sub- V1 suprathreshold
V5 sub- V1 subthreshold
V5 suprathreshold only
V1 suprathreshold only
Phosphene report
3.0
2.5
2.0
1.5
1.0
0.5
0.0
–80
–60
–40
–20
0
20
40
60
80
V5 TMS precedes V1 TMS
V1 TMS precedes V5 TMS
TMS SOA (ms)

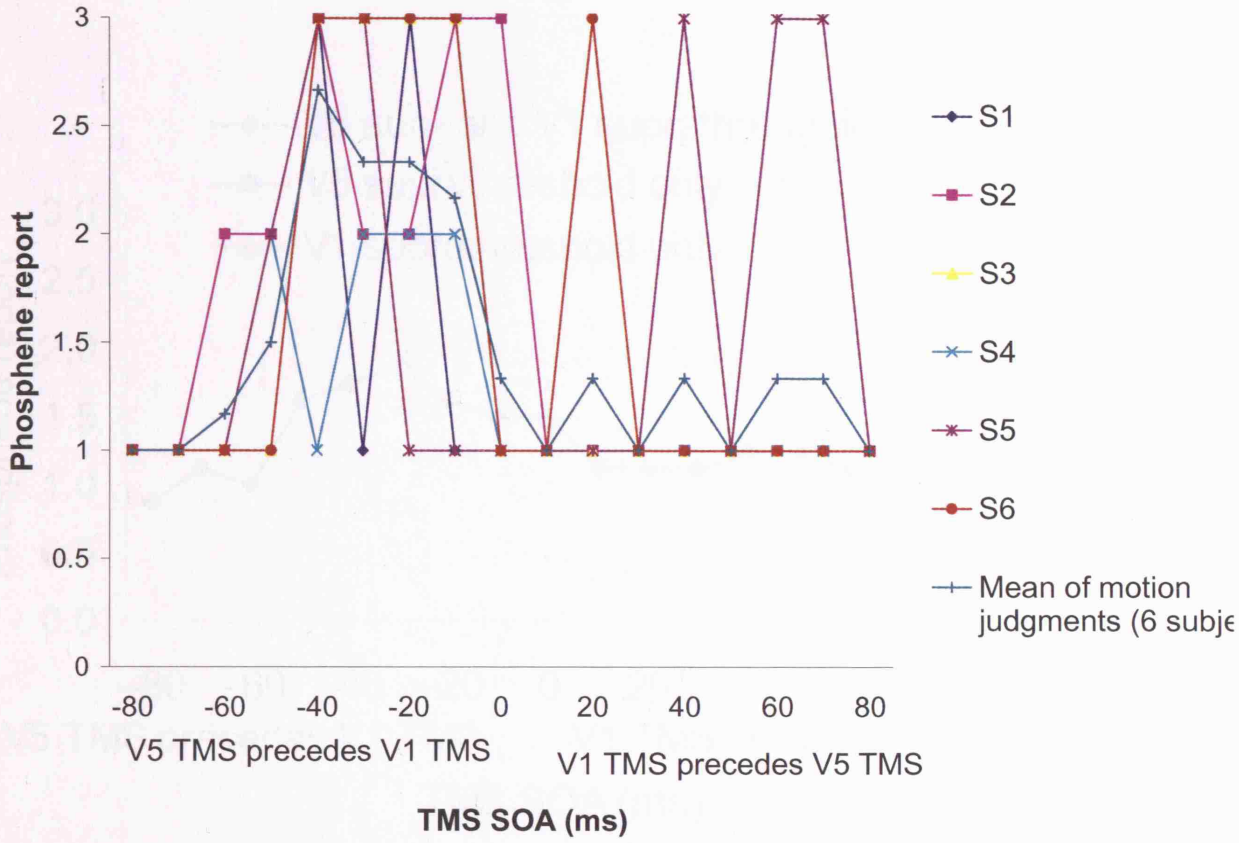
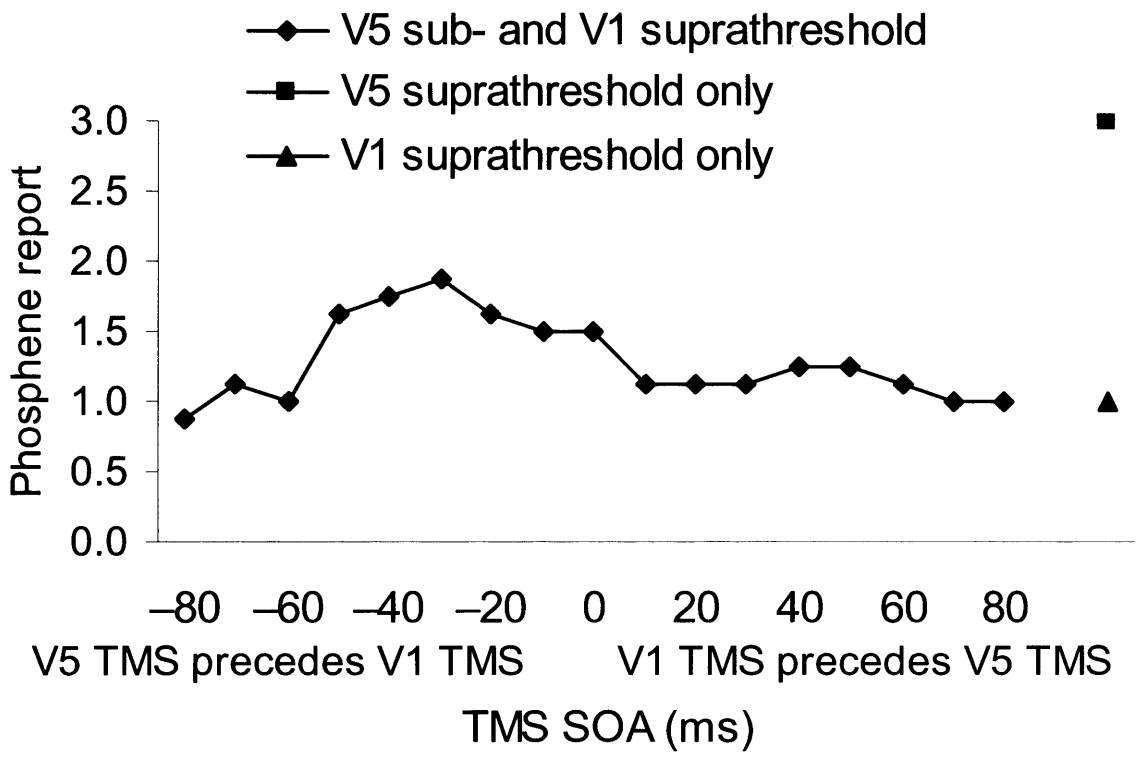


Figure 4.1. *Motion judgments of subjects (n=6) who perceived moving phosphenes when V5 was stimulated alone at suprathreshold level. Subjects were asked to judge whether (0) phosphene was absent; (1) phosphene was stationary; (2) uncertain whether phosphene was moving or stationary; (3) the phosphene was moving. The scale was adapted from Pascual-Leone and Walsh (2001). When TMS was applied over V5 at subthreshold level 40 ms before V1 was stimulated at suprathreshold level, five of the six subjects reported the perception of moving phosphenes. The lower figure shows the judgments of each subject for the critical V5 sub- V1 suprathreshold condition.*


V5 sub- and V1 suprathreshold
V5 suprathreshold only
V1 suprathreshold only
Phosphene report
3.0
2.5
2.0
1.5
1.0
0.5
0.0
–80 –60 –40 –20 0 20 40 60 80
V5 TMS precedes V1 TMS
V1 TMS precedes V5 TMS
TMS SOA (ms)

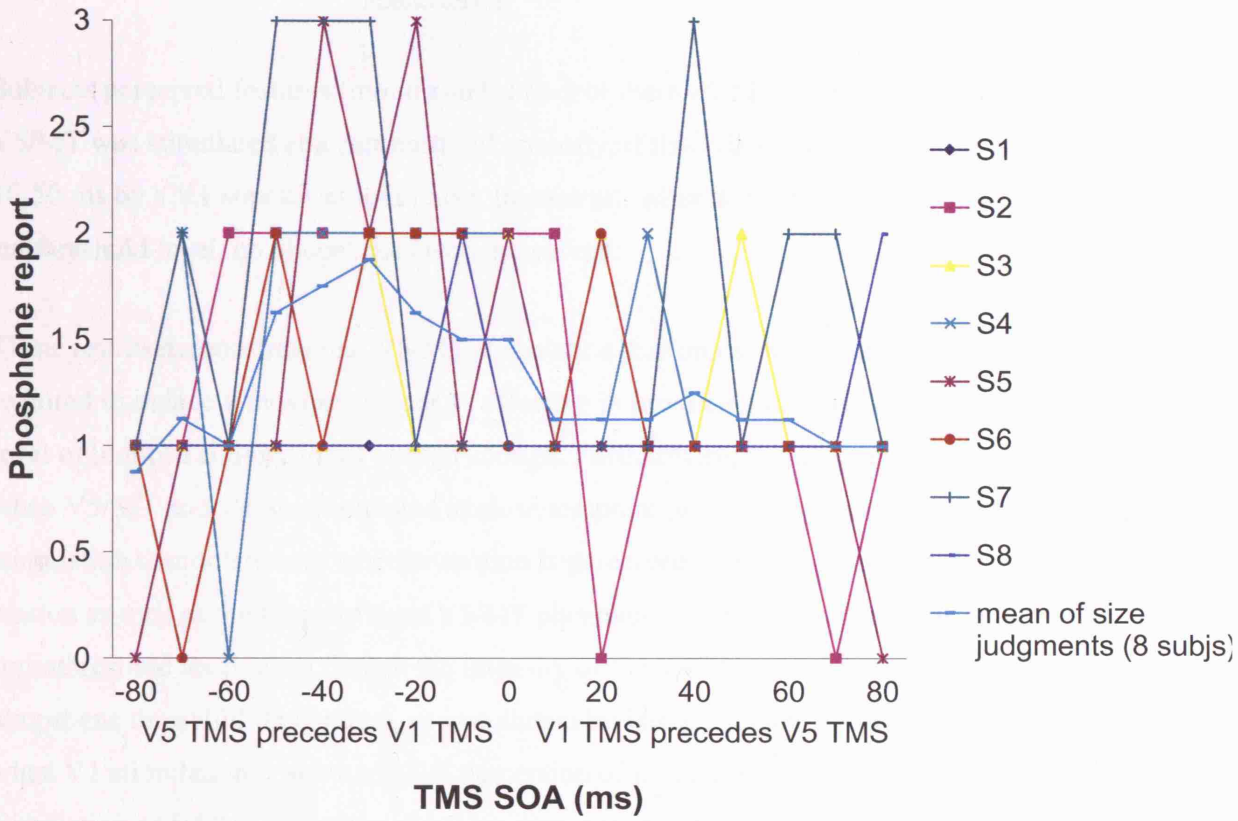


Figure 4.2. *Shape/size judgments in Experiment 1. Subjects (n = 8) were asked to judge whether their percept was like a (1) V1 phosphene; (2) mixture of V1 and V5 phosphenes; (3) V5 phosphene; subjects responded (0) when phosphene was absent. Five of the eight subjects perceived a mixture of V1 and V5 phosphenes when TMS was applied over V5 30 ms before V1. The lower figure shows the judgments of each subject for the critical V5 sub- V1 suprathreshold condition.*

Discussion

Subjects perceived features (motion and shape) of their V5/MT phosphene even when V5/MT was stimulated at a subthreshold intensity, if this stimulation was followed by 10-50 ms by a V1 suprathreshold pulse. In contrast, when both sites were stimulated at subthreshold level, no phopshenes were perceived.

These results demonstrate that V5/MT stimulation that on its own is below the level required to induce a moving percept, is effective in producing a moving percept if the level of induced activity in V1 is high enough. Furthermore, in this context (that is, when V5/MT and V1 are stimulated at close temporal proximity) it is the level of V1 stimulation that determines whether motion is perceived: subjects always perceive motion as well as the shape of their V5/MT phosphene when V1 is stimulated at a suprathreshold level, even though the intensity of the V5/MT stimulation was below phopshene threshold. In contrast, as was shown by Pascual-Leone and Walsh (2001), when V1 stimulation is subthreshold, perception of motion induced by suprathreshold stimulation of V5/MT is suppressed. This demonstrates the importance of the level of activity in V1 in determining the *presence* of awareness, and that the *content* of awareness is characterised by backprojections from extrastriate areas.

The finding that only when suprathreshold V1 stimulation follows but not precedes subthreshold V5/MT stimulation are moving phosphenes perceived, together with the gradual increase in motion perception from 10 ms to 50 ms period, precludes a simple feedforward summation account in terms of feedforward projections triggered by V1 TMS boosting the activation level of V5/MT above phosphene threshold. Conceivably, the subthreshold V5/MT activity might persist long enough to be physiologically enhanced by feedforward from V1 following the second pulse of TMS to V1, but if this were the case suprathreshold V1 TMS prior to V5/MT TMS should have elicited awareness of motion, which it did not. Instead, the time course of the present result points to a critical time of backprojection arrival in V1. A more complex feedforward summation account in which V5/MT activity is primed with subthreshold TMS before summation with a feedforward input from a suprathreshold V1 stimulation remains

logically possible for the present finding when taken in isolation. However, the results of Chapter 1 that V1 stimulation has an effect on motion perception both before and after the critical V5/MT stimulation period but V5/MT stimulation only affects motion perception at one time period before the second V1 period, makes this account unlikely because the priming account predicts that V5/MT stimulation effects should postdate the latest of V1 effects. Furthemore the narrow time window for V5/MT -V1 interaction in the present study (10-50 ms) is consistent with previous reports of extrastriate-striate feedback interactions in motion in humans (Pascual-Leone & Walsh, 2001) and monkeys (Hupe et al, 2001).

It might seem that the method of applying TMS over two visual areas is too artificial to provide an insight into real motion perception: how could activation level of V1 be higher than that of V5/MT, if V1 is driven by backprojections from V5/MT? In real vision, motion stimuli are encoded not only by V5/MT, but also by various other extrastriate areas that encode the shape and colour of the moving stimulus. If these all project stimulus-related information back to V1, it is clear that the activation level in V1 will be higher than in any one extrastriate area. In contrast, if two extrastriate areas project conflicting information to V1, perception cannot arise due to the resulting inhibition in V1, no matter how high the activation level in the extrastriate areas. This is consistent with the findings that V1 neurons can integrate various stimulus attributes (Gruenwald & Skoumbourdis, 2004). This integration is manifested from the onset of V1 responses, as are the effects of feedback from V5/MT (Hupe et al, 2001).

In summary, these experiments showed that even though backprojections from V5/MT to V1 determine the content of awareness, it is the activation level of V1 rather than V5/MT that determines whether that information reaches awareness.

Chapter 5: Conscious perception of visual qualia in the absence of V1

Introduction

Destruction of the primary visual cortex (V1) abolishes all visual awareness in the corresponding part of the visual field, but in some cases an ability to detect stimuli in the blind field does remain (Poeppel et al, 1973; Sanders et al, 1974). This phenomenon, referred to as blindsight (Sanders et al, 1974) was first demonstrated by Poppel et al (1973) who showed that patients were able to make saccades towards visual targets in the absence of any visual experience. Pointing was subsequentely found to be an even more accurate measure in revealing blindsight (Sanders et al, 1974). Blindsight has been demonstrated with attributes such as wavelength (Stoerig & Cowey, 1992), orientation discrimination (Weiskrantz & Cowey, 1971; Morland et al, 1996) and motion with a single moving bar or spot (Azzopardi & Cowey, 2001). That a stimulus which the subject knew was delivered, and under certain circumstances detects, is not accompanied by a phenomenal visual experience is the hallmark of blindsight that makes it intriguing to students of visual consciousness (Cowey, 2004). The visual abilities that survive the lesion in humans (and even in monkeys who receive daily training for many years after the lesion) are so impoverished that the subjects are clinically blind, but that any remain at all despite the complete lack of visual awareness points to a dissociation between visual processing and visual awareness that places V1 center stage in understanding awareness.

The seemingly unique role of V1 in visual awareness is supported by the finding that the blindsight subject GY was unable to perceive visual sensations (phosphenes) when intact regions of his damaged hemisphere are stimulated (Cowey & Walsh, 2000). In contrast, phosphenes could readily be induced from GY's intact hemisphere, as well as from the visual cortex of a totally retinally blind subject with severed optic nerves but an intact V1. Stimulation which consistently induced phosphenes from GY's

contralesional hemisphere and in a retinally blind patient, but was unable to do so when applied to GY's ipsilesional visual cortex demonstrates that even directly induced extrastriate activity does not easily or, cannot, reach awareness in the absence of V1. This view is supported by demonstrations of the necessity of V5/MT-V1 backprojections in the conscious perception of TMS-induced moving phosphenes (Pascual-Leone & Walsh, 2001) as well as visually presented stimuli in normal subjects (findings of Chapter 3), and it is central to many current theories of awareness (e.g. Lamme, 2001; Pollen, 1999, 2003; Hochstein & Ahissar, 2002). This importance of V1 for the phenomenal visual consciousness is supported by evidence that palinopsia (pathological visual persistence or illusory re-appearance) disappears after V1 lesions (Bender et al., 1968), complex hallucinations induced by temporal lobe damage do not intrude into a field defect caused by damage to V1 (Gloning et al 1967), and patients who experience visual phosphenes in a hemianopic field have damage to the visual radiations rather than to V1 itself (Kölmel, 1984). However, there are several counter-examples where densely hemianopic patients have reported hallucinatory phenomena within a field of cortical blindess (see Stoerig and Cowey, 1997).

Even though stimulation of GY's ipsilesional V5/MT does not by itself give rise to conscious percepts when stimulated on its own, it remains possible that under certain circumstances this activation can reach awareness via the intact hemisphere. Activity in GY's ipsilesional V5/MT induced by moving stimuli presented in his blind field is transmitted to his contralesional V5/MT (ffytche, 2001), and as V5/MT contains a partial representation of the ipsilateral hemifield that extends up to 15 degrees from the vertical meridian (Zeki, 1974; Raiguel et al, 1995), perhaps visual information corresponding to GY's blind field can reach awareness in his intact hemisphere. I studied this possibility by stimulating GY's ipsilesional V5/MT while inducing phosphenes from his contralesional V5/MT (Experiments 1 and 2) or V1 (Experiment 3).

Experiment 1

Methods

Subjects

The blindsight subject GY suffered almost total destruction of his left V1 by a vascular incident following a traffic accident at the age of 8, with some additional damage to extrastriate areas V2 and V3, and his damaged V1 shows no responsiveness to visual stimulation (Barbur et al, 1993; Baseler et al, 1999; Azzopardi & Cowey, 2001). While GY does have some spared macular striate cortex, it is not activated by stimuli that elicit blindsight corresponding to absent parts of striate cortex (Stoerig et al, 1998). He has up to 4 degrees of macular sparing in his blind (right) visual field.

Whether GY has some phenomenal vision in his blind field has been a matter of some controversy. GY is often aware that something has occurred but this is not accompanied by any visual sensations – this is referred to as Blindsight Type 2 (Weiskrantz, 1997) – and has been sometimes taken to imply that GY's percept is comparable - albeit degraded – to normal vision. For instance, an imaging study Barbur et al (1993) reported on the neural correlates of "conscious perception without V1", but in retrospect GY stated that the visual stimuli in that study never gave rise to the perception of visual qualia (Weiskranz, 1997), and described his sensation as "black on black...but nothing like real vision". In attempts to gain insight to the phenomenal nature of this experience, GY has been asked to match his blind field percept with stimuli presented in the good field. The study does report that a match was possible. However it is questionable whether GY would have made a match at all if he had not been to forced to make one. Afterwards GY has remarked that he experienced no phenomenal qualities in that study. GY's awareness without visual sensation is likely to result from learning to associate physiological responses to visual stimuli with presentation of those stimuli (Cowey, 2004). For instance, it is possible the blindsight subject learns to associate, over

hundreds of trials eye movements triggered by a certain stimulus with the presentation of that stimulus.

Five neurologically normal subjects (three males and two females, mean age 31.5 years) acted as control subjects.

Transcranial Magnetic Stimulation

Two MagStim Rapid stimulators (MagStim, Wales) and 70 mm figure-of- eight coils were used for stimulation. TMS was delivered over V5/MT as determined from structural scans and imaging data (Goebel et al, 2001). The skull coordinates with respect to the inion were 3 cm dorsal and 5 cm for the left V5/MT and 3 cm dorsal and 5.3 cm lateral for the right V5/MT. The coil orientation was such that the handles were horizontal and pointing away from the midline.

Stimulation onset asynchronies ranging from -80 ms (i.e. magnetic stimulation applied first to the normal hemisphere) to + 80 ms (i.e. magnetic stimulation applied first to the damaged hemisphere), in steps of 10 ms. Trials that included only the contralesional V5/MT pulse were included to serve as a comparison to GY's percepts at each SOA condition.

In the first two testing sessions, the contralesional (right) V5/MT was stimulated at phosphene threshold (69%) and the ipsilesional (left) V5/MT at 80 % of the stimulator's maximum output, which was the highest intensity at which GY experienced no discomfort such as twitching. Control subjects were stimulated using the same parameters (i.e. right V5/MT at phosphene threshold and left V5/MT at 80 %). In the third session, GY's contralesional (right) V5/MT was stimulated initially 10% and then 5 % below phosphene threshold. Again, control subjects were stimulated with the same parameters.

Procedure

Initially, the phosphene thresholds in GY's contralesional V5/MT were determined using a binary search paradigm (Tyrrell & Owens, 1988). The phosphene thresholds were re-measured at the end of testing and they showed reassuring consistency: the pre- and post-testing values for the single pulse stimulation were 69 % / 71 %. The mean phosphene thresholds of the normal subjects were 63% and 62% for pre- and post-testing, respectively.

Subjects were asked to close their eyes during stimulation and did so. The centre of a sheet of paper directly in front of the subject at a distance of 42 cm served as an imaginary fixation point, on which subjects were asked to draw the phosphenes induced by both the contralesional only- stimulation and the bilateral stimulation in relation to the felt fixation point after each SOA condition. In all experiments, five trials were given for each SOA condition. In addition, three contralesional-only TMS trials were conducted prior to each SOA condition to provide a comparison for the phosphenes that were perceived with bilateral stimulation.

Results

The objective of Experiment 1 was to determine whether TMS applied over GY's ipsilesional V5/MT while a phosphene is induced from his contralesional V5/MT enables the ipsilesional activation to enter awareness. Single-pulses of TMS were applied over the two sites at stimulation onset asynchronies ranging from -80 to +80 ms, with the intact V5/MT stimulated at phosphene threshold.

Whereas single pulses of TMS administered over V5/MT of either hemisphere of a normal subject induces a phosphene in the contralateral visual field (Figure 5.1.A), and simultaneous stimulation of the two sites induced two distinct phosphenes, one in each hemifield, stimulation of the two sites with stimulation onset ansynchronies ranging from 10 to 60 ms induced a single unified, bilateral phosphene (See figure 5.1.B).

In GY, unilateral stimulation of V5/MT in the intact hemisphere induced a phosphene similar to those reported by normal subjects (Figure 5.2.A.). Consistent with an earlier report (Cowey & Walsh, 2000), unilateral stimulation of the ipsilesional did not induce phosphenes. In contrast, the bilateral stimulation of V5/MT induced a unified bilateral phosphene in GY at a similar range of SOAs. These phosphenes had the appearance of a white arc and they intruded 6 to 10 degrees into both hemifields (see Figure 5.2.B). GY could not confidently judge whether the speckled phosphenes were moving in a coherent direction but almost always described them as being bilaterally symmetrical. Across two testing sessions, strong bilateral phosphenes were consistently induced with stimulation SOAs ranging from 10 – 60 ms (both when the contralesional pulse preceded and followed the ipsilesional pulse) with strongest effects observed at SOAs between 10 and 30 ms. However, with simultaneous stimulation GY's percept was the same as when his contralesional V5/MT was stimulated on its own. As expected, the contralesional stimulation by itself always induced a phosphene that was restricted to GY's good hemifield. But in the absence of contralesional stimulation, TMS administered over the ipsilesional V5/MT never induced phosphenes, even when he was stimulated at the maximum output of the stimulator.

I also investigated whether GY's blind field can support conscious perception when the intact hemisphere is stimulated at intensity insufficient on its own to elicit a phosphene. When the contralesional V5/MT was stimulated below phosphene threshold (at first by 10 % below and then by 5 %), GY never perceived phosphenes in either the good or the blind field at any of the SOAs. Increasing the intensity of the ipsilesional stimulation from 80% to 100% of maximum stimulator output had no effect, implying that the lack of blind field phosphene could not be due to a decrease in overall activation level of the ipsilesional visual cortex. In contrast, normal subjects could still perceive bilateral phosphenes when one V5/MT was stimulated 5% and 10% below phosphene threshold.

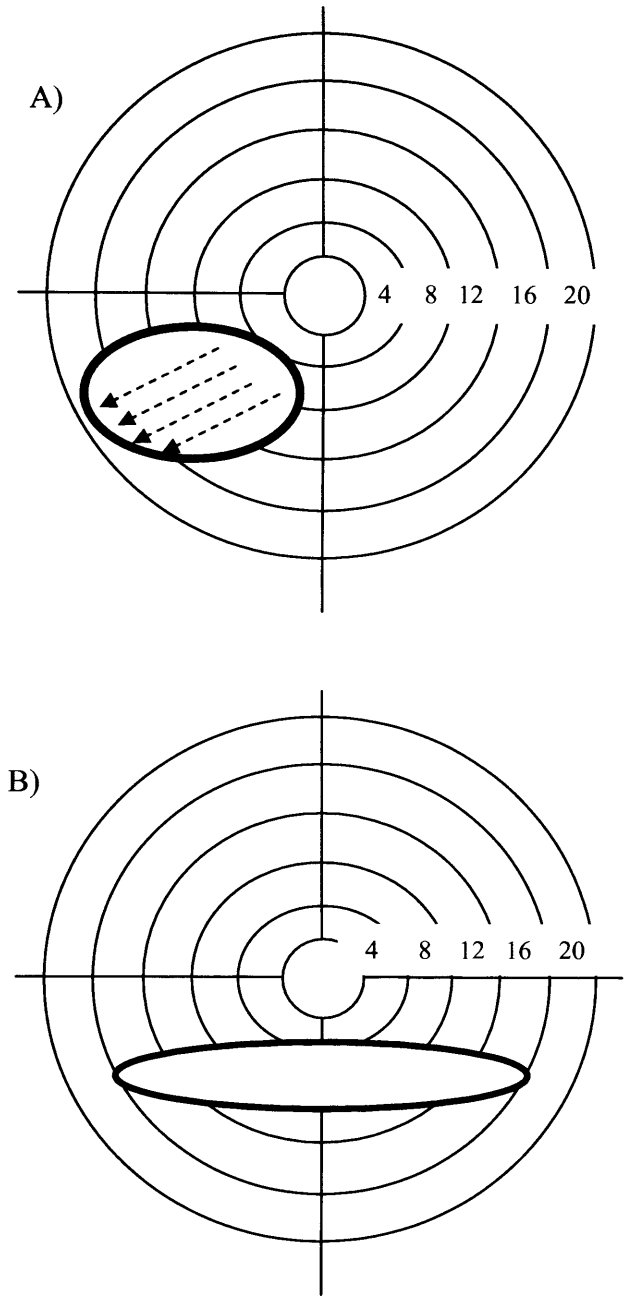
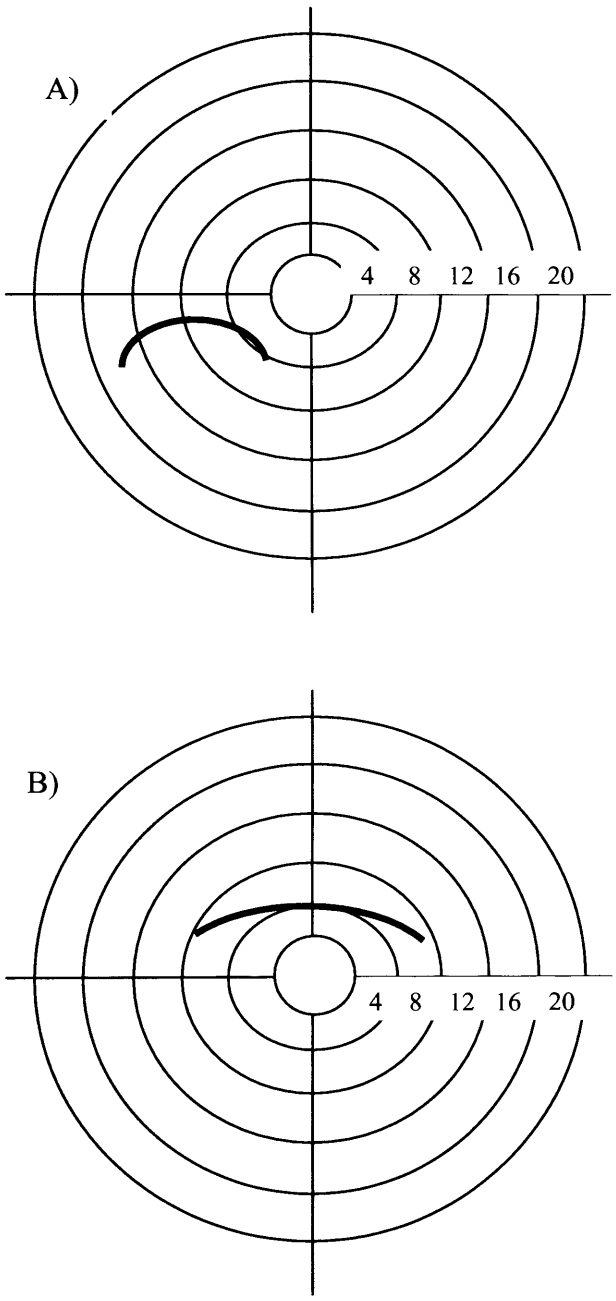


Figure 5.1. *Schematic examples of phosphene appearance in one representative control subject. (A) With unilateral stimulation of either hemisphere, the subject perceived a moving phosphene in the contralateral hemifield. The arrows represent the perception of motion. (B) With bilateral stimulation of V5 at stimulation onset asynchronies ranging from 10-60 ms, the subject perceived a unified, static bilateral*

percept. The static nature of the bilateral phosphene is likely to reflect the summation of two phosphenes moving in opposite directions. The numerals indicate degrees of eccentricity.



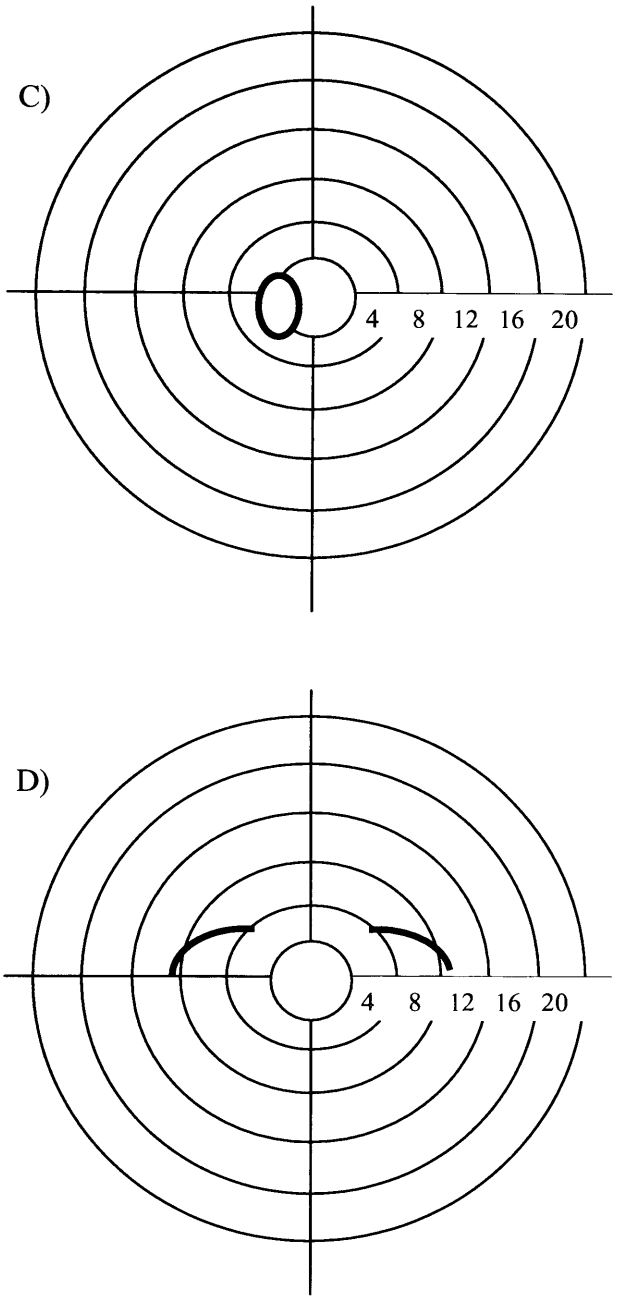


Figure 5.2. *Phosphene appearance in GY. (A) With unilateral stimulation of GY's contralesional V5, he perceived phosphenes similar to those reported by normal subjects. (B) With bilateral V5 stimulation, GY perceived a phosphene that intruded 6-10 degrees into his blind field. These appeared either in the upper (as shown) or lower visual field. (C). Stimulation of GY's contralesional V1 induced a small phosphene*

close to fixation. Numerals indicate degrees of eccentricity. (D). Bilateral TMS with tripulses applied bilaterally over GY's V5 induced bilateral phosphenes that were not joined..

In summary, Experiment 1 showed that GY can experience qualia in his blind field as a part of a unified bilateral percept when his V5/MT was stimulated bilaterally. However, when the contralesional V5/MT was stimulated below phosphene threshold, GY perceived no phosphenes, suggesting that the presence of a good field percept is prerequisite for conscious perception in his blind field.

Experiment 2

Experiment 1 demonstrated that GY can perceive qualia in his blind field as a part of a bilateral percept when his V5/MT is stimulated bilaterally. However he perceived no phosphene when the contralesional V5/MT was stimulated below phosphene threshold, suggesting that his blind field percept can only arise as part of a bilateral phosphene

The objective of Experiment 2 was to investigate whether GY's can perceive phosphenes in his blind field even when the contralesional V5/MT is stimulated below phosphene threshold, if the induced activation is of a longer duration. To address this possibility, area V5/MT was stimulated bilaterally with pulse trains (3 pulses at 33 Hz, i.e. a pulse gap of 30 ms) rather than with single-pulses.

Methods

Subjects

GY and four neurologically normal subjects (two males and two females, mean age: 33.8 years) were tested.

TMS and Procedure

TMS was administered over both sites at 33 Hz (i.e., 3 pulses in 90 ms; pulse gap of 30 ms). Stimulation onset asynchronies (i.e., the time gap between the last pulse of one pulse train and the first pulse of the other) were studied from -60 ms to +60 ms in steps of 20 ms, and conditions in which the pulse trains were either interleaved (i.e., one pulse train beginning 30 ms before the other) or simultaneous were also included. Trials that included only the contralesional V5/MT pulse were included to provide a comparison with GY's percepts at each SOA condition. GY's phosphene threshold with these stimulation parameters was 65 %. The contralesional (right) V5 was stimulated 5% below phosphene threshold, and the ipsilesional (left) V5 at 80% Normal subjects were stimulated with same parameters. Stimulation and procedure were otherwise identical to that in Experiment 1.

Results

When the intensity of the contralesional V5/MT stimulation was 60%, 5% below the phosphene threshold of 65% for these stimulation parameters, GY still perceived white, bilateral arc-like phosphenes. Unlike the bilateral phosphenes that were elicited in the single pulse- paradigm, the percepts in the two fields were not joined together, even though they were symmetrical in shape (see figure 5.2.). Bilateral phosphenes were elicited at SOAs ranging from -40 (i.e. the last pulse of the first pulse train preceding the first pulse of the second pulse train by 40 ms) to +40 ms and they lay within the blind field at eccentricities ranging from 8 to 15 degrees of visual angle. However, GY did not consistently perceive phosphenes that were restricted to the blind field. When the ipsilesional V5/MT was stimulated on its own at the maximum output of the stimulator as well as with 40 Hz tripulse TMS using 80 % of maximum output, he never perceived phosphenes.

As the sub threshold TMS over the contralesional V5/MT never induced phosphenes when administered without the ipsilesional stimulation, GY's perception of bilateral phosphenes implies that that the ipsilesional stimulation facilitated conscious perception in the good field. Further testing revealed that with these stimulation parameters TMS over the ipsilesional, left V5/MT could bring subsequent sub threshold stimulation of the contralesional right V5/MT to perceptual threshold at SOAs up to 100 ms in four normal subjects this occurred at SOAs ranging from 140 – 220 ms, with a mean of 170 ms). GY also reported the impression of apparent motion that was induced by a dot-like phosphene appearing at first in the good field and then in the blind field with the contralesional stimulation at 55%, 10% below phosphene threshold, at SOAs of +20 and +40 ms (TMS applied first over the ipsilesional V5). When stimulation intensity of the contralesional V5/MT was reduced further, to 10% below phosphene threshold, GY no longer perceived phosphenes. This suggests that the presence of a phosphene in G.Y.'s good field is a necessary requirement for phosphene perception in his blind field.

Experiment 3

The objective of Experiment 3 was to study the role of G.Y.'s contralesional V1 in generating phosphenes in his blind field. The functional connectivity between the ipsilesional V5/MT and contralesional V1 was probed by determining whether stimulation of the ipsilesional V5/MT can modulate the appearance of phosphene induced from the contralesional V1. As in Experiment 2, tripulses of TMS were applied at 33 Hz.

Methods

Subjects

G.Y. and four neurologically normal subjects (two males and two females, mean age 33.8 years) were studied.

Stimulation and procedure

G.Y.'s ipsilesional V5/MT and contralesional V1 were stimulated using the procedure and stimulation parameters of Experiment 2. The phosphene threshold of the contralesional V1 at these stimulation parameters (i.e. tripulses at 30 Hz) was 70%. The contralesional (right) V1 was stimulated either at phosphene threshold or 5% below it. The ipsilesional (left) was stimulated at V5 at 80%. Normal subjects were stimulated with same parameters (that is, right V1 at or 5% below phosphene threshold and left V5 at 80%).

TMS was administered over both sites at 30 Hz (i.e., 3 pulses in 90 ms; pulse gap of 30 ms). Stimulation onset asynchronies (i.e., the time gap between the last pulse of one pulse train and the first pulse of the other) were studied from -100 ms to +100 ms in steps of 20 ms, and conditions in which the pulse trains were either interleaved (i.e., one pulse train beginning 30 ms before the other) or simultaneous were also included. Trials that included only the contralesional V1 pulse were included to serve as a comparison to G.Y.'s percepts at each SOA condition. In other respect the stimulation and procedure were identical to those in Experiments 1 and 2.

Results

In normal observers, stimulation of V5/MT never influenced the appearance of the phosphene induced by contralateral V1 stimulation. However in GY, when TMS over the intact V1 was at phosphene threshold, TMS over the ipsilesional V5/MT influenced the appearance of the good field V1 phosphene: V1 TMS by itself produced a small, amorphous phosphene close to fixation (see Figure 5.2.). However with the ipsilesional V5 stimulation, GY perceived an arc extending approximately 8-15 degrees into his good field, of similar appearance to the phosphenes induced in the good field with unilateral V5/MT stimulation of the intact hemisphere (see Figure 5.2.) and he often reported the sensation of motion. This occurred when the V5/MT stimulation preceded

V1 stimulation by up to 60 ms (i.e. a gap 60 ms between the last pulse of the V5 TMS and first pulse of the V1 TMS) and when the V1 TMS preceded V5 TMS by up to 40 ms.

When TMS over the intact V1 was administered 5-10 per cent below phosphene threshold, GY did not perceive phosphenes, even when the ipsilesional V5/MT was stimulated at 80 per cent of the maximum stimulator output, an intensity that in Experiment 2 lifted the sub threshold stimulation of the contralesional V5/MT to beyond perceptual threshold. That the stimulation of these two sites interacted to change the appearance of the phosphene points to an abnormal functional connectivity between them. In contrast to GY, in normal subjects stimulation of V5/MT and V1 interact only when these sites are stimulated in the *same* hemisphere.

Discussion

In agreement with an earlier result (Cowey and Walsh, 2000) GY perceived phosphenes in his normal, left, visual hemifield when TMS was applied to his right V5/MT but never perceived a phosphene in his blind hemifield when TMS was applied only to V5/MT of his damaged hemisphere. In striking contrast he experienced bilateral phosphenes when the area V5/MT was stimulated bilaterally, regardless of which site was stimulated first. To the best of our knowledge this is the first report of conscious perception of visual qualia in the blind field of a blindsight subject.

Interestingly, GY did not consistently perceive phosphenes that were restricted to his blind field. In Experiment 1, when the contralesional hemisphere was stimulated below phosphene threshold, GY perceived no phosphenes, implying that the presence of a phosphene in his good field phosphene is necessary for a blind field percept. In Experiment 2, when pulse trains (rather than single-pulses as was done in Experiment 1) were used, GY still perceived bilateral percepts *despite* sub threshold stimulation of the contralesional V5/MT, indicating that the input from the ipsilesional hemisphere

boosted the activation level of the contralesional V5/MT to perceptual threshold. When the stimulation intensity of the latter was further decreased, GY no longer perceived phosphenes, reinforcing the conclusion that GY can only perceive phosphenes in his blind field as part of a bilateral phosphene.

The need for a stimulation onset asynchrony between the two V5/MT pulses suggests that for a bilateral phosphene to arise in both GY and in normal observers, activation induced by the first TMS pulse needs to reach the contralateral hemisphere before the latter is stimulated. This contralateral input is likely to increase the activation level (alter the sensitivity) of neurons with receptive fields encoding the ipsilateral visual field, and when the second TMS pulse is applied, these pre-activated neurons could be brought to perceptual threshold, hence giving rise to a bilateral percept. This suggestion that TMS can alter the sensitivity of distal anatomically connected regions is supported by the finding that TMS applied over the frontal eye fields increases the sensitivity (assessed by the phosphene threshold) of V5/MT (see Chapter 6). Furthermore, the view that the present results reflect information transfer from GY's ipsilesional V5/MT to its contralesional counterpart is consistent with evidence that activation induced by visually presented moving stimuli in GY's blind field can cross from his ipsi- to the contralesional V5/MT (ffytche, 2001).

Recordings in V5/MT in macaques have shown that the receptive fields of V5 invade the ipsilateral hemifield (Zeki, 1974; Raiguel et al, 1994), as do neurons in V1 (Cowey, 1964). That GY's bilateral phosphenes never extended beyond the extent of the ipsilateral representation in V5/MT (up to 15 degrees of visual angle from the vertical meridian; Raiguel et al, 1995), whereas in normal subjects phosphenes induced from V5/MT often extend further, is consistent with role of this ipsilateral representation in generation of GY's blind field percepts. A further aspect of GY's bilateral phosphene also support this view: in the monkey, nasotemporal overlap of retinal ganglion cell projections can extend 5-9 degrees in the lower periphery and approximately 15 degrees in the upper periphery, whereas it is narrow in the central retina (Fukuyama et al, 1989), suggesting that the visual cortex contains a representation of the ipsilateral visual field

that extends further in the upper and lower periphery. The location of GY's phosphenes mirrors this arrangement: his phosphenes only intruded into the blind field in the lower or upper part of the hemifield, and not at the fovea. Also consistent with this is the finding that in Experiment 2, when GY's intact hemisphere was stimulated below phosphene threshold, the component of the phosphene nearest to the fovea disappeared while the more peripheral components remained, giving rise to a disunified bilateral percept (see Figure 5.2.D.). This might reflect a weakening of the ipsilateral representation as one moves from the periphery towards the fovea.

What are the anatomical pathways that mediate GY's ability to perceive qualia in his blind field? The most obvious candidate for this interhemispheric pathway is via the corpus callossum (Maunsell & Van Essen, 1983a). However, while GY's corpus callosum has not been sectioned, he does have pronounced atrophy of callosal fibres in the fornix major, and it has been argued that a non-callosal pathway mediates this interhemispheric information transfer (ffytche et al, 2001).

A recent study by Leh et al (2006), using diffusion tensor imaging (DTI), found that in hemispherectomised subjects who display blindsight the superior colliculus showed both ipsi-and contralateral connectivity from the superior colliculus to various cortical regions, whereas in normal subjects as well as in hemispherectomised subjects who did not show blindsight these connections are predominantly ipsilateral. Given that GY sustained his lesion at the age eight, it is possible that comparable reorganization has taken place in his brain. Relevant to this discussion is the finding that TMS applied over GY's ipsilesional V5/MT modulated the appearance of phosphenes induced from his contralesional V1. In normal observers such an interaction did not occur when V5/MT and V1 were stimulated in different hemispheres. This implies an abnormal functional connectivity between these two sites, and points to the importance of the contralesional V1 in enabling GY's ipsilesional activation to reach awareness. How this abnormal connectivity is reflected at the anatomical level remains to be seen.

These findings are not inconsistent with the view that V1 is necessary for awareness, as they reiterate the view that GY's ipsilesional hemisphere is unable to support conscious perception. However, at first sight, the timing of the effects in the single-pulse paradigm seems to argue against this view. The finding that GY perceives bilateral phosphenes when the ipsilesional V5 TMS precedes the contralesional stimulation is perhaps not surprising, as this information can then be projected to the V1 in the same hemisphere where it can reach awareness (cf. Pascual-Leone & Walsh, 2001). But that this also occurs when the ipsilesional stimulation postdates the contralesional stimulation is more surprising, as it suggests that the involvement of the ipsilesional V5 postdates that of the contralesional V5. However, this is a not a problem for the view that it is the intact V1 that mediates GY's blind field phopshenes: as was shown in Experiment 3, the ipsilesional V5/MT and the intact V1 can interact even when the contralesional V5 is not stimulated. Furthermore, the abnormal functional connectivity between the ipsilesional V5/MT and the contralesional V1 might reflect anatomical abnormalitites, and inferring cortico-cortical interactions from the timing of TMS effects in such circumstances is problematic.

A second possibility is that it is the interaction between the two V5/MT's that enabled conscious perception in GY's blind field, without the contralesional V1 playing any part. In this account, there is nothing unique about V1; rather, it is cortico-cortical interactions that give rise to visual awareness. Extrastriate-striate connections are most suitable for this, but if the recurrent activity between two extrastriate areas is artificially enhanced, awareness can arise.

On the current evidence it is not possible to distinguish between these two explanations. This issue can be resolved by combining TMS with functional neuroimaging: by comparing the fMRI or EEG response of bilateral vs. intact field phosphenes in GY would indicate the brain regions that are selectively activated when GY perceives phosphenes in his blind field. That it is the intact V1 that enables conscious perception in GY's blind field is a possibility that is supported by the abnormal functional connectivity between the contralesional V5/MT and the intact V1. Future studies

combining TMS with neuroimaging techniques such as EEG will help to determine the contralesional regions that are critical for GY's blind field percepts.

Chapter 6: Modulation of V5/MT activity by stimulation of frontal eye fields

Introduction

The human frontal eye fields (FEF) are part of a putative control network in which areas in the frontal and parietal lobes are thought to influence the sensitivity of neuronal responses in secondary visual areas (Gitelman et al, 1999; Hopfinger et al., 2000; Giesbrecht et al., 2003). Many studies have examined the parietal component of this network but fewer have concentrated on the FEF. Early studies of the effects of lesions to the macaque FEF show that this area is required for normal performance on complex tasks such as visual search (Latto and Cowey, 1971; Collin et al, 1982) and recording studies have subsequently demonstrated a role for the FEF in visual detection tasks. For example, Thompson and Schall (1999) recorded activity in monkey FEF neurons in a backward masking detection task. Activity of FEF neurons following the target presentation was greater for both hits and false alarms at late latencies indicating a role in motor decisions, but at short latencies (beginning around 40 ms –60 ms) however FEF activity was greater following the presentation of a target regardless of subjects' reports (i.e. for misses as well as hits) indicating a role in visual registration.

Moore and Fallah (2001) found lower luminance detection thresholds following electric stimulation of monkey FEF neurons 50-175 ms before the onset of a visual stimulus in the motor receptive field of the FEF neuron. However, it is not clear whether the improvement in detection was mediated by a direct change in sensitivity of the FEF neuron or by FEF stimulation activating connecting neurons in other areas, such as extrastriate or parietal cortex. A follow-up study of FEF - V4 interactions (Moore & Armstrong, 2003) showed that the sensitivity of neurons in extrastriate area V4 was increased if microstimulation was applied to the FEF if the end point of the saccade vector of the FEF neuron undergoing stimulation fell within the receptive field of the V4 neuron. This study has been interpreted as evidence of top-down modulation of V4 by FEF and also as supporting the premotor theory of attention (e.g. Smith et al., 2005) because it shows an association between eye movements and covert attention.

However, microstimulation was applied for only 50 ms between 200 and 500 ms after visual stimulus onset. In other words the stimulus had been in the vector field of the FEF neuron for a significant period during which the monkey was attending to the visual stimulus, covering the time period both of visual processing and saccade preparation. Further, the microstimulation was only applied during a period when the monkey was preparing an eye movement to the stimulus. These two aspects of the experiment preclude any dissociation of sensory modulation from eye movement preparation (Juan et al, 2004).

To examine the extent to which the findings from non-human primate physiology could be applied to the human cortex, Grosbras & Paus (2003) stimulated the human frontal eye fields in a backward masking task and found that TMS applied 40 ms prior to the target onset improved detection sensitivity. However, as the authors note, it is possible that in this study the FEF were rendered more sensitive to incoming information rather than having an effect on the sensitivity of extrastriate visual areas. Moreover the presentation of a visual stimulus to the retina and therefore through the geniculostriate pathway means that one cannot infer a specific effect of FEF stimulation on any particular visual area. More recently, Taylor et al (2006) applied TMS over the FEF and simultaneously measured occipital visual evoked potentials (ERPs) while subjects performed a covert orienting task. They recorded from electrodes placed on the same hemsiphere as the TMS stimulation and observed that the FEF TMS changed the responses of the visual cortex. They concluded that the "FEF exerts a causal influence over activity in the visual cortex" during voluntary orienting of attention.

Taken together, these lines of evidence (Moore & Fallah 2001; Moore & Armstrong 2003; Grosbras & Paus 2003; Smith et al, 2005, Taylor et al, 2006) suggest that visual cortex sensitivity is modulated by FEF. To demonstrate this directly in humans and to explore the hemispheric organisation of FEF – sensory cortex interactions, I induced activity in the FEF via transcranial magnetic stimulation (TMS) and measured subjects' sensitivity to phosphenes induced by TMS over V5/MT. By locally inducing phosphenes with V5/MT stimulation and hence bypassing the LGN and striate cortex I

was able to obtain a direct measure of the sensitivity of a specific extrastriate visual area – MT/V5. I show that stimulation of FEF 20-40 msecs prior to stimulation of V5/MT decreases the intensity of V5/MT stimulation required to elicit a visual percept and therefore that the sensitivity of human V5/MT is modulated by activity levels in the FEF. To control for site specificity I also applied TMS to the vertex (i.e. top of the skull) and V5/MT at the same asynchronies as in the FEF condition and to control for temporal specificity I applied TMS at seven different time points.

Methods

Subjects

Nine subjects (five males and four females, mean age 28.5 years) took part in the investigation, eight of whom were naïve to its purpose. Seven subjects were tested in each condition, with five subjects in taking part in both right and left FEF TMS sessions. The subject who was not naive to purpose (J.S.) was naïve to the timing of the TMS pulses, as was the experimenter and all other subjects. The study was approved by the local ethics committee, and subjects gave informed consent. All subjects had previously participated in studies of phosphene perception, the advantage being that their phosphene thresholds are stable.

Transcranial magnetic stimulation

TMS was administered with two Magstim Super Rapid stimulators (Magstim Company, UK). The pulses were triggered remotely using a computer that controlled both stimulators, using E-Prime software. 50 mm figure-eight coils were used over both sites. The stimulation strength was always the same over FEF and Vertex, 65%, an intensity that has been used in many previous FEF studies (e.g. Muggleton et al, 2003; O'shea et al, 2004) and is known to induce behavioural effects. Subjects were seated on a chair designed for massage so that the subject's head and body weight were forward and the head rested in a cushioned hole which allowed the face to peer through. The head is more stable in this arrangement than in a conventional head and chin rest. The

coils were fixed in place using "magic arm" (Manfrotto) coil holders. Subjects' eyes were covered throughout the experiment and they were instructed to simply report whether or not they had perceived a phosphene after each TMS pulse. All subjects reported phosphenes that were restricted to the visual field contralateral to stimulation of V5. To control for temporal specificity I applied TMS at seven different time points. Specifically, TMS pulses were delivered at FEF/Vertex - V5/MT stimulation asynchronies between -60 ms (FEF/Vertex TMS preceding V5/MT TMS) and +60 ms (V5/MT TMS preceding FEF/Vertex TMS) in steps of 20 ms (Figure 6.1.). After each TMS delivery, subjects reported verbally whether or not they had perceived a phosphene. To determine phosphene thresholds for each TMS condition the intensity of V5/MT pulse was varied according to a modified binary search (MOBS, Tyrell & Owens, 1998), an adaptive threshold finding algorithm. The TMS intensity was increased or decreased according to the subject's report on the previous trial. The original upper boundary of the stimulation was 100% of stimulator output and the lower limit 0%. The number of trials required for setting a threshold depends on the consistency of the subject's reports and in this experiment was between 6 and 20 trials. Intertrial interval was determined by the subject's speed of response and was approximately six seconds per trial.

TMS Localisation

TMS was applied over locations that corresponded with the anatomical delineation of left and right FEF (Figure 6.1.) and left and right MT/V5 (Watson et al, 1993; Dumoulin et al. 2000) by structural MRI in each subject (see Muggleton et al., 2003 and O'Shea et al., 2004 for details). For MT/V5 an additional criterion was the induction of moving phosphenes (Stewart et al, 1999).Vertex was used as an additional control stimulation site to control non-specific effects of TMS. The stimulation sites were identified on each subject's T1-weighted MRI scan and coregistered with scalp co-ordinates. FEF was determined anatomically as lying over the posterior middle frontal gyrus, rostral of the junction of the precentral sulcus and the superior frontal sulcus (Paus, 1996; Blanke et al., 2000). In terms of scalp measurements the average position of stimulation was 5cm lateral of the saggital midline and 3-4cm anterior of the hand

area. This site corresponds well with previous studies (Muggleton et al., 2003; O'Shea et al, 2004) and those of others (Leff et al., 2001; Muri et al., 1991). Mean Talairach co-ordinates were 32, -2, 47 for the right FEF and -32, -2, 46 for the left FEF (Talairach & Tournoux, 1988; Paus, 1996). V5 can be accurately determined from the production of moving phosphenes (Stewart et al., 1999) and we also determined this using Brainsight co-registration (following Campana et al, 2002, 2005).

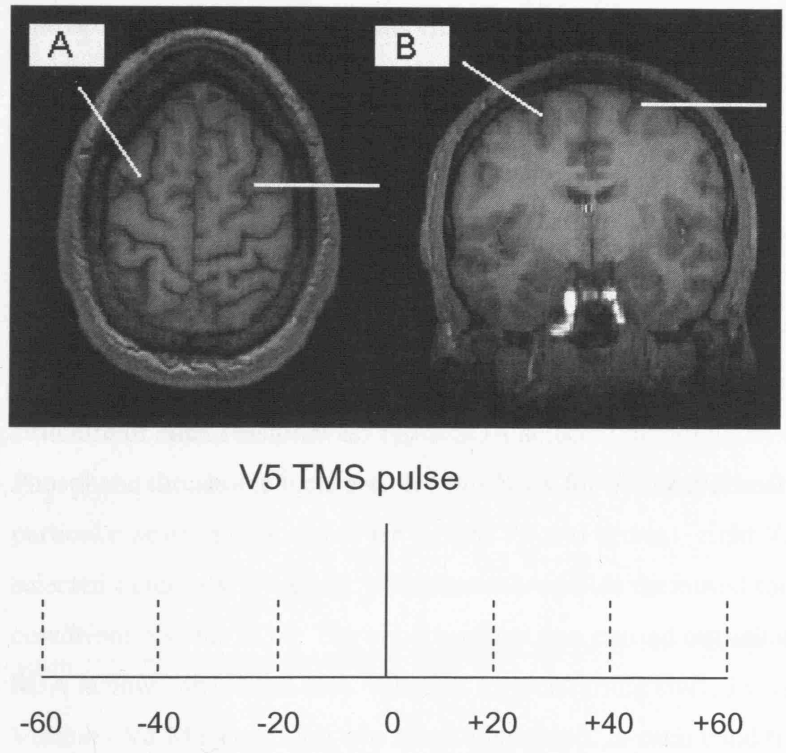


Figure 6.1. *A) and B) Transverse and coronal views indicating the location of the left and right frontal eye fields in one subject. C) Timeline of an experimental trial. On all trials, a TMS pulse was applied over V5/MT. A second pulse of TMS was applied,*

depending on the experimental condition, over either FEF or vertex at an SOA between -60 ms (stimulation preceding the V5/MT pulse) and +60 ms (stimulation postdating the V5/MT pulse). A trial with a particular combination of stimulation site (FEF; Vertex) and SOA (-60 ms; -40 ms; -20 ms; 0 ms; +20 ms; +40 ms; +60 ms) was repeated until the phosphene threshold had been successfully determined for that condition using a Modified Binary Search Paradigm. This required between 6 and 15 trials. FEF and Vertex were always stimulated with an intensity of 65% of the maximum output of the stimulator.

Procedure

The order of the TMS conditions was intermixed pseudo-randomly, so that a condition in which FEF TMS preceded or followed V5/MT TMS by a given time window was followed by a condition in which vertex TMS preceded or followed V5/MT TMS in the same time window, and vice versa. There were three experimental sessions and in each session two conditions were carried out: One session consisted of Right FEF – right V5 and Vertex – right V5 conditions, another consisted of right FEF – left V5 and Vertex – Left V5, and another consisted of left FEF – right V5 and left FEF – left V5 conditions. Within and between each session the order of TMS conditions was randomized. The structure of each session was: 1) An SOA selected randomly by the software. 2) Phosphene thresholds measured for this SOA for both experimental conditions in that particular session (e.g. right FEF – right V5 and vertex – right V5). 3) The next SOA selected randomly. 4) Again, phosphene thresholds measured for both experimental conditions for this SOA. The condition that was carried out second for the previous SOA is now carried out first. Whether a given timing started with an FEF – V5/MT or Vertex – V5/MT condition was counterbalanced. In each condition, the phosphene threshold was determined once using the binary search paradigm, which takes between 6-20 trials. As there were 7 SOAs (-60, -40, -20, 0, 20, 40, 50) and six experimental conditions (right FEF – right V5; vertex – right V5; right FEF – left V5; vertex – left V5; left FEF – right V5; left FEF – left V5), the phosphene threshold was measured a total of 42 times (14 times in each session), with an average of 12 trials required for

each threshold. In addition, the baseline threshold (in which TMS was applied only over left or right V5/MT) was measured a total of 16 times (8 times for each V5). Baseline thresholds were measured at the beginning and the end of each session, as well as after the fifth and ninth TMS/Vertex conditions (as was mentioned above, their were 14 threshold conditions in each session). The mean values of the baseline thresholds were 60 and 65 percent of the maximum stimulator output for left and right V5/MT respectively. Stimulations of left and right V5/MT were carried out on separate days. No vertex condition was run in comparison with the left FEF condition based on the prediction from Grosbras and Paus (2003) that there would be left-right field differences in the effects of left FEF stimulation (specifically a null prediction for the left FEF stimulation) and previous evidence that right and left FEF TMS have different effects on visual processing in the two visual fields (Muggleton et al., 2003).

Results

Subjects' phosphene thresholds in each condition were measured as a percentage of the maximum output of the stimulator unit. To obtain a relative measure of the phosphene thresholds, subjects' absolute thresholds in the FEF and Vertex condition were normalised relative to the baseline threshold level in that session.

TMS over right FEF

The application of TMS to right hemisphere FEF decreased phosphene thresholds in both right and left V5/MT. Figure 6.2.A. shows normalised phosphene thresholds of right V5/MT TMS as a function of each TMS condition. For the right V5/MT TMS a within-subjects ANOVA with stimulation site (FEF, vertex) and stimulation onset asynchrony (-60, -40, - 20, 0, + 20, + 40, + 60) as factors indicated a significant interaction between stimulation site and timing ($F(1,6) = 3.549$; $p = 0.007$, MSE = 0.0026). A paired-sample t-test revealed that FEF stimulation applied 20 ms before the V5/MT pulse significantly lowered the phosphene threshold in comparison to vertex stimulation at the same time window ($t(6) = 5.012$; $p = 0.002$; Standard Deviation =

0.069; SEM= 0.026). In contrast, there was no statistically significant difference between the FEF and Vertex conditions when their stimulation postdated the V5/MT pulse by 20 ms (t(6) = 0.323; p = 0.390; SD = 0.105; SEM = 0.023).

The normalised phosphene thresholds of left V5/MT as a function of each right FEF and vertex TMS condition, averaged across the seven participants, are shown in Figure 6.2.B. For the left V5/MT TMS a within-subjects ANOVA with stimulation site (FEF, vertex) and stimulation onset asynchrony as factors indicated a significant interaction between stimulation site and time window ($F(1,6) = 3.305$; $p = 0.017$, Mean Square of Error = 0.0047). Pairwise comparisons revealed that FEF stimulation preceding the MT/V5 pulse by 40 ms significantly lowered subjects' phosphene thresholds in comparison to vertex stimulation in this time window ($t(6) = 3.01$; $p = 0.024$; SD = 0.126; SEM = 0.048). In contrast, the difference between the two conditions was not statistically significant when their stimulation postdated the MT/V5 pulse by 40 ms (t(6) = 0.795; p = 0.457; SD = 0.076; SEM = 0.029). It is apparent in Figure 6.2.B. that the facilitatory effect of right FEF TMS on the activity of left V5/MT is moderately present at SOAs that precede and postdate the time window of the strongest effect. However, at these time windows the difference between the FEF and Vertex conditions was not statistically significant for (20 ms: ($t(6) = 1.752$; $p = 0.130$; SD = 0.143; SEM = 0.054; 60 ms: $t(6) = 1.774$; $p = 0.126$; SE = 0.072; SEM = 0.027).

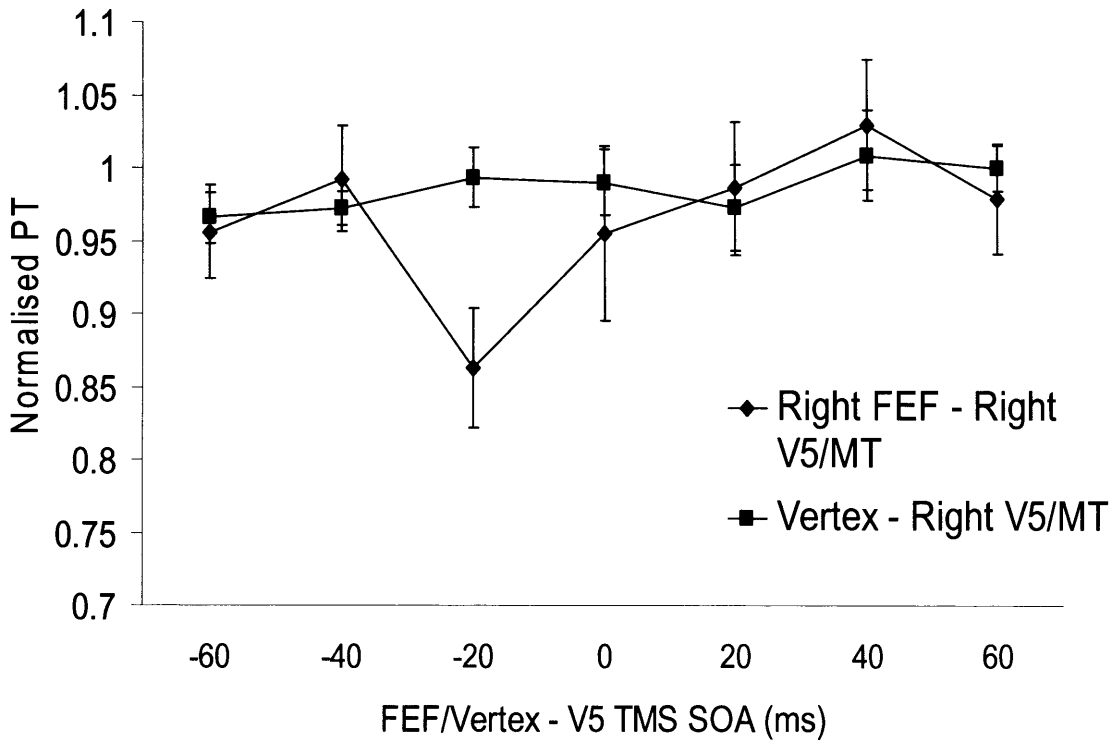


Figure 6.2A). *Mean of normalized phosphene thresholds (PT) (n = 7). All error bars indicate +/-1 SEM. Transcranial magnetic stimulation of the right frontal eye fields (diamond symbols) lowered the phosphene threshold of ipsilateral V5/MT, with the peak of this effect occurring when TMS was applied over the FEF 20 ms before V5/MT was stimulated. TMS over Vertex (squares) had no effect.*

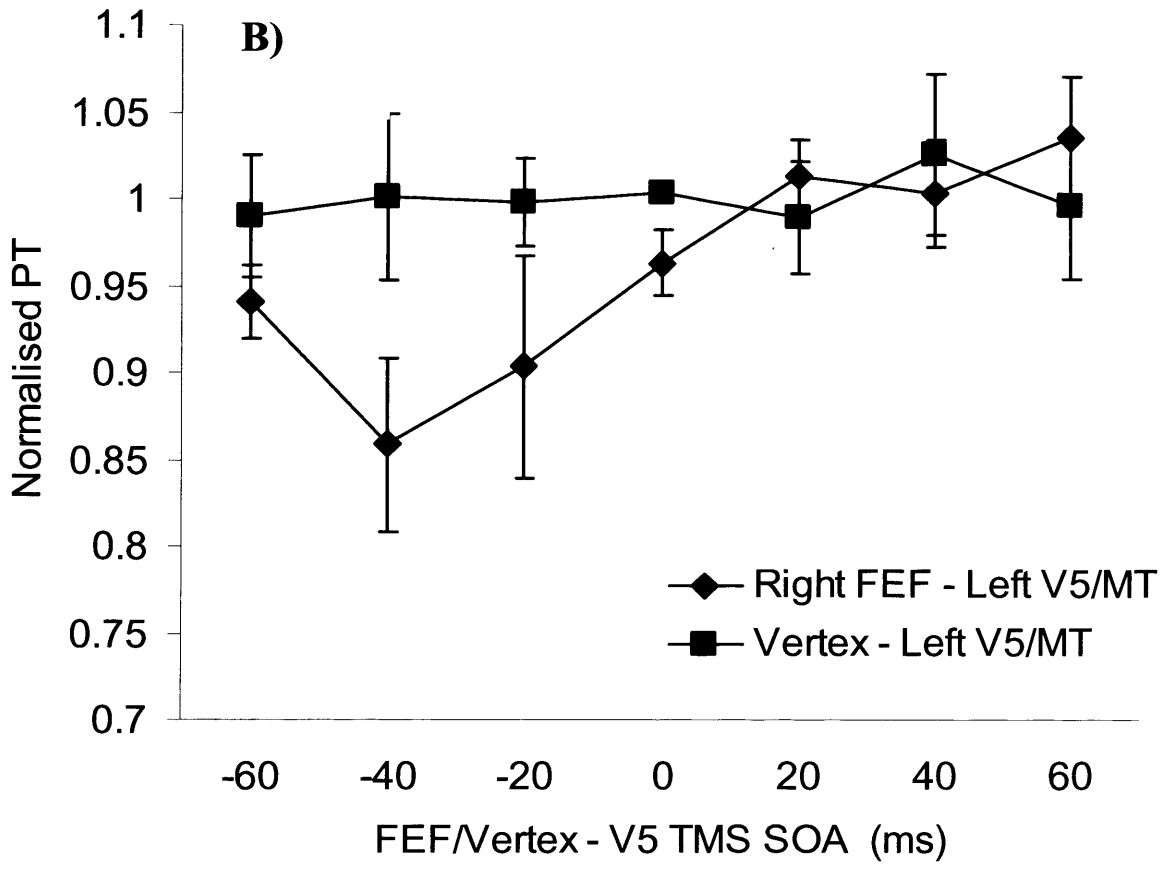


Figure 6.2.B) *Mean of normalized phosphene thresholds (PT) (n = 7). All error bars indicate +/-1 SEM. Transcranial magnetic stimulation of the right frontal eye fields (diamond symbols) lowered the phosphene threshold of contralateral V5/MT, with the peak of this effect occurring when TMS was applied over the FEF 40 ms before V5/MT was stimulated. TMS over Vertex (squares) had no effect.*

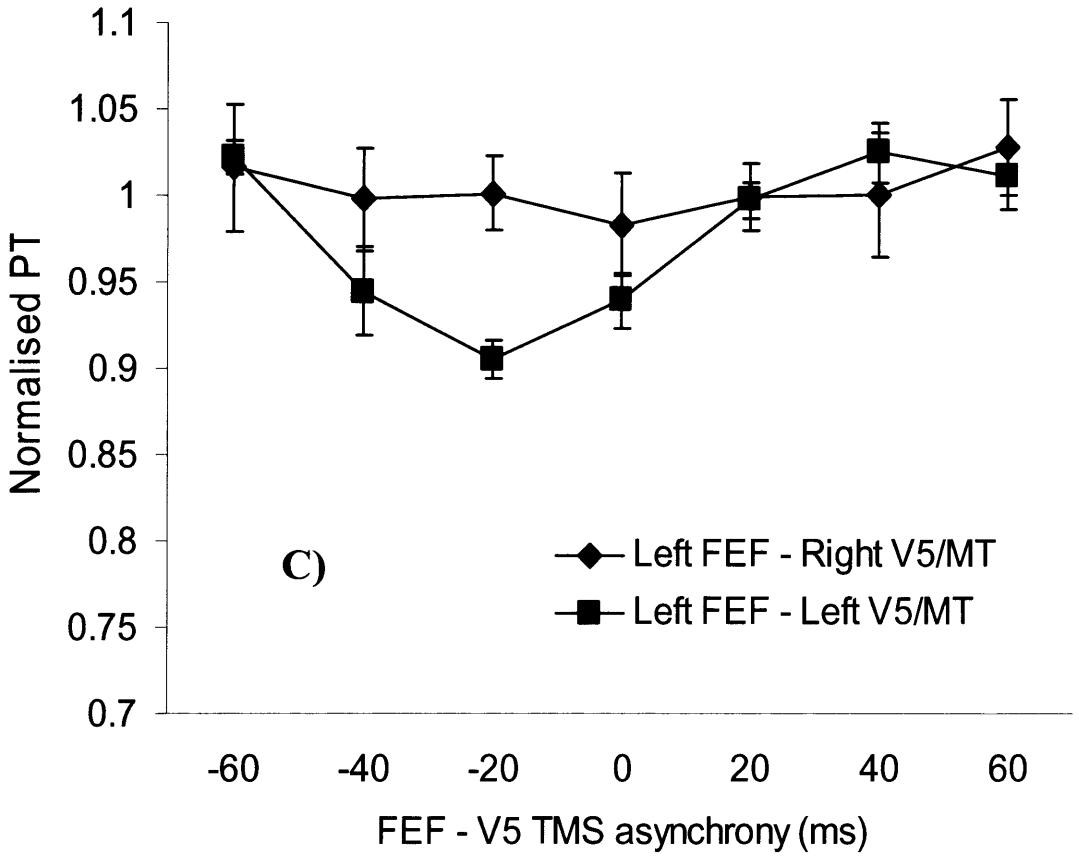


Figure 6.2.C. *Mean of normalized phosphene thresholds (PT) (n = 7) of V5/MT in the each experimental condition. All error bars indicate +/-1 SEM. Ipsilateral but not contralateral effects of left FEF TMS on cortical sensitivity: TMS applied over the left FEF lowered the phosphene threshold of the ipislateral V5/MT (squares) but not contralateral visual cortex (diamonds).*

TMS over left FEF

Figure 6.2.C. shows normalised phosphene thresholds of right and left V5/MT TMS as a function of each FEF TMS condition. The application of TMS to left FEF decreased phosphene thresholds in left but not in right V5/MT. A within-subjects ANOVA with phosphene stimulation site (Left vs. right V5/MT TMS) and FEF stimulation onset asynchrony as factors indicated a significant interaction between phosphene stimulation site and SOA (($F(1,6) = 3.402$; $p = 0.009$; MSE = 0.0018). A paired-sample t-test revealed that FEF stimulation applied 20 ms before the left V5/MT pulse significantly lowered the phosphene threshold in comparison to right V5/MT TMS at the same time window (t(6) = 6.148; p =0.001; SD= 0.0387; SEM= 0.0146). In contrast, there was no statistically significant difference between the right V5/MT and left MT/V5 conditions when their stimulation postdated the V5/MT pulse by 20 ms (t(6) = 0.832; p = 0.437; SD = 0.10; SEM = 0.376).

Again, a moderate facilitatory effect of left FEF TMS on the activity of left V5/MT is present at SOAs that precede and postdate the time window of the strongest effect. However, at these time windows the difference between the FEF and right V5/MT condition was not statistically significant for the left MT/V5 condition (-40 ms: $t(6)$ = 2.126; p = 0.078; SD = 0.103; SEM = 0.039; 0 ms: $t(6) = 2.088$; $p = 0.082$; SD = 0.094; SEM = 0.036).

Discussion

These results clearly show that activity in the human FEF modulates the excitability of extrastriate visual cortex. Together with the findings of Grosbras and Paus (2003), Taylor et al (2006), Smith et al (2005), Thompson and Schall (1999) and Bullier (2001),

this data suggest that one of the saccade-independent functions of FEF is to exert top down modulation over extrastriate visual cortex. Several studies have now shown that some FEF responses are independent of saccade command signals and it is these visual rather than motor FEF neurons that have been associated with top down control and attention. The content of the top down control may be either spatial or feature-related. Thompson et al (2005), for example have identified spatially selective enhanced activity in visual FEF neurons during a covert spatial attention task and a concurrent suppression of activity in FEF movement neurons. They concluded that "selective activity in FEF visually responsive neurons corresponds to the mental spotlight of attention via modulation of ongoing visual processing". Other recording studies (e.g. Bar et al, 2005) have shown that some visual FEF neurons' responses are correlated with the identity of the target and it is therefore possible that FEF visual neurons are involved in both spatial and object-related processes in selective attention tasks. Bar et al., (2005) have presented evidence from Magnetoencephalography (MEG) and fMRI studies for an early top-down role for FEF in visual object processing. Greater activation in FEF was seen when subjects were presented with objects they successfully recognised than for objects they did not. This activity preceded activity in visual object recognition areas by 30 msecs (see, O'Shea et al., 2004, O'Shea & Walsh, 2006). Whether this early FEF activity in reflects top down control processes dedicated to space, object features or both remains to be determined. With regards to how FEF exerts top-down control, it is possible that FEF activity occurs prior to sensory stimulation as opposed to rapid responses to visual stimuli (cf a possible role for FEF neurons in visual priming: Bichot & Schall, 2002). It is important to note that the term "top-down" is used in the temporal context of FEF receiving visual information prior to the extrtastriate areas, but it remains entirely possible that top down processes are mediated by a feed forward anatomical connection from, say FEF to V4 (eg Barone et al., 2000).

The frontal eye fields are part of the fronto-parietal network involved in many aspects of vision but as was noted in the introduction, the role of the FEF has not received the same attention as that of the PPC. To understand the function of the FEF within this network, however, requires a description of the similarities and differences between

these two major nodes. One aspect of the present findings reflects the well established hemispheric asymmetry in attentional functions in humans: i.e., that the right hemisphere is more commonly concerned with processing information in both visual fields, whereas the left hemisphere appears to be concerned only with the right visual field (e.g. Mesulam, 1981). That right FEF TMS decreased phosphene thresholds in both visual fields whereas left FEF TMS only decreased phosphene thresholds in the right visual field is consistent with this and adds to the many examples of similarities between the organisation of FEF and PPC in vision and attention. For example, frontal and parietal areas have both been shown to produce neglect when damaged (Keating & Gooley, 1988; Mesulam, 1999); have both been shown to be important in detecting abrupt changes in the visual field (Beck et al 2001, 2005; Turatto et al, 2004); and have been shown to be important in visual search (Donner et al., 2000; Nobre et al., 2003). Demonstrating differences between the two nodes, however, is a less common finding and my result may have implications in this regard. I interpret the effects of FEF TMS on extrastriate activity to be evidence of a top down role for FEF because it is consistent with a role for the early visual activity of FEF visual neurons (Murthy et al., 2001). An area involved in control would be expected to be active early and by responding to target features, the FEF could increase the sensitivity of extrastriate neurons to task relevant parameters (e.g. Moore & Armstrong, 2003; Moore & Fallah 2001). These findings may also help to understand why a recent TMS study obtained only equivocal evidence of a role for the PPC in top down control (Hung et al., 2005): damage to the frontoparietal network may only result in a disruption of top down modulation if the early input to the FEF is disrupted. Both frontal and parietal nodes may be important for aspects of visual orienting and awareness and there are reports of early visual responses, attributed to attentionl processes in both. Bisley et al (2005), for example, recently reported rapid responses to visual stimuli of neurons in lateral intraparietal cortex (LIP) and Fuggetta et al. (2006) reported that TMS over the PPC after onset of a visual search display can eliminate the N2pc component associated with target detection. This was interpreted as evidence of TMS interfering with spatial processes in the search task. Both FEF and PPC, then, have been associated with spatial top down processing but a major difference between them seems to be that the FEFs have also been associated

with feature processes. Some physiological properties of the FEF may make it well placed to exert feature-related top down influence: the FEF responds to visual stimuli very rapidly and is part of what has been called "the fast brain"(Bullier, 2001; O'Shea et al., 2004); the organisation of FEF-visual cortex connections is retinotopic (Schall et al, 1995); FEF neurons show distinct feature-related activity (Thomspon & Schall, 1999) and a preference for stimuli that are relevant as targets (Schall & Hanes, 1993); and pre-activation of the FEF improves visual detection with the same spatial pattern of hemispheric specialisation as found in the current study (Grosbras & Paus 2003) and influences attention-related activity in the visual cortex (Taylor et al., 2006). Further, comparison of the effects of FEF vs PPC stimulation using a partial report task designed to probe top down control has shown that human FEF is important for target rather than distractor processing (Hung, 2005). The pattern of hemispheric asymmetries is an important component of interpreting the role of the FEF in humans and the present effects show that the right FEF needs approximately 20 msec longer to influence the contralateral than the ipsilateral visual cortex, presumably due to callosal transmission time.

In summary, these findings extend and complement the microstimulation studies of non-human primate FEF (Moore & Fallah 2001; Moore & Armstrong 2003) and the magnetic stimulation study of Grosbras and Paus (2003) in showing that FEF activity modulates the responses of visual cortex in a manner consistent with a role in top down control of visual processing.

Chapter 7: General Discussion

7.1. Importance of V5/MT-V1 feedback in perception of visual motion stimuli

Three types cortico-cortical interactions between V1 and V5/MT have been suggested to give rise to awareness of motion. According to the "microconsciousness" account (Zeki & Bartels, 1999) activity in any secondary visual area is sufficient to generate a conscious visual percept without requiring any feedback activity in V1. In motion detection this account has lead to suggestions that activation of V5/MT is sufficient for motion awareness: once motion information has reached V5/MT, V1 is no longer necessary for motion detection. An alternative possibility put forward by Pollen (1999) is that the synchronous activity between visual areas that are involved in the processing of a stimulus is necessary for awareness to arise, and V1 is particularly important when fine details are involved. The prediction from this theory is that the phenomenal experience of a particular attribute requires near-simultaneously experienced percepts in a number of cortical areas involved in the processing of that stimulus (Pollen, 1999). A third possibility (Lamme, 2001) is that there is a qualitative difference between feedforward and feedback activity in V1, and that the late period of V1 activity, in response to feedback connections from extrastriate areas, gives rise to awareness. The objective of the experiments described in Chapter 3 was to distinguish between three major theories of V1-V5/MT interactions in awareness of motion. This was achieved by administering TMS over V1 or V5/MT in different time windows during performance of a motion detection task in order to trace the flow of information that gives rise to awareness.

The results showed two critical periods of V1 activity, one preceding and another postdating the V5/MT critical period, suggesting that although V5/MT obtains visual information through V1 feedforward activity (reflected in the early V1 critical period predating that of V5/MT), backprojections from V5/MT to V1 remain critical for awareness of motion, as demonstrated by the presence of the late V1 critical period

postdating that of V5/MT. This finding demonstrates the importance of backprojections in normal vision and shows that the role of V1 extends beyond the feedforward sweep and is inconsistent with the view that activity in an extrastriate area selective for a particular attribute is sufficient for awareness of that attribute (Zeki & Bartels, 1999). They also argue against the possibility that perceiving a visual stimulus requires simultaneous activity in all visual areas involved in processing of that stimulus (Pollen, 1999). However it is possible that when subjects are asked to report more than one stimulus attribute (such as a conjunction of colour and motion), synchronous activity across the visual cortex becomes important. Furthermore, moving objects in normal vision tend to consist of complex shapes and non-uniform colours (e.g., cars) and it is therefore possible that the synchronous activity theory is more reflective of normal vision than is suggested by these psychophysical experiments.

It would seem that the findings of experiments described in Chapter 4 are most consistent with the view that feedforward and feedback activity reflect qualitatively different types of processes, with only the latter being critical for awareness (Lamme, 2001). However these findings are also consistent with theories that place importance to extrastriate-V1 feedback in visual processing in general, rather than awareness in particular. It has been suggested that feedback activity is particularly important in computing local details in images that cannot be computed by the large receptive fields of extrastriate neurons (Bullier, 2001; Hochstein & Ahissar, 2002; Pollen, 1999). In these models, awareness of global representations of the visual field, provided by extrastriate areas precedes awareness of local details computed in V1. The present findings are not inconsistent with these theories, as the experimental task may have required computation of local details in V1 because the motion was across very short distances (each dot moved only one pixel between the frames), and it could be argued that the need for fine spatial detail necessitated the recruitment of small receptive fields of V1. This could be tested by using larger stimuli that move across large distances. In practice, however, this would be difficult to test as TMS applied over V1 disrupts a relatively small area of the visual field. The finding that large phosphenes induced by V5/MT TMS with motion components spanning almost a whole hemifield can be

disrupted by a subsequent subthreshold V1 TMS pulse (Pascual-Leone & Walsh, 2001), however, does argue against the possibility that only the perception of small motion vectors is dependent on V5/MT-V1 backprojections.

7.2. Activation level of V1 as the determinant of awareness of motion

Disruption studies such those described in Chapter 4 can demonstrate that a brain area is necessary in a given cognitive process, but it cannot necessarily tell why that is the case. For this reason, the opposite approach was adapted in experiments described in Chapter 2. Rather than attempting to disrupt motion, the objective was to induce a moving percept even though V5/MT was stimulated at subthreshold level. Specificially, these experiments had two objectives. Firstly, to directly demonstrate that activation of V5 reaches awareness via V1, and secondly, to study whether the activation level of V1 determines whether that information reaches awareness. This was done by studying the effect of stimulation intensity over V1 on subjects' reports of phosphene motion. The main findings were that subjects perceived features (motion and shape) of their V5 phosphene even when V5/MT was stimulated at a subthreshold intensity, if this stimulation was followed by 10-50 ms by a V1 suprathreshold pulse. In contrast, when both sites were stimulated at subthreshold level, no phosphenes were perceived, and when both sites were stimulated at suprathreshold level, subjects again perceived qualities of both phosphenes. Taken together with the findings of Pascual-Leone and Walsh (2001), who found that suprathreshold TMS of V5 does not produce moving phosphenes if V1 is stimulated at subthreshold level, it can be concluded that the activation level of V5 does not determine whether motion is perceived; even though V5 influences information content in V1 via feedback connections, it is the activation level of V1, and not that of V5/MT, that determines whether motion is consciously perceived. This conclusion that V1 acts as the gatekeeper of conscious motion perception is also consistent with the fact that GY is unable to perceive phosphene when TMS is applied unilaterally over his ipsilesional V5/MT. From a theoretical point of view, these findings are most consistent with Lamme's (2001) proposal of a qualitative difference

between feedforward and feedback modes of visual processing, as this account proposes a key role in visual awareness for V1 activity in response to feedback from extrastriate areas. In contrast, these findings are difficult to reconcile with the microconsciousness theory put forward by Zeki and Bartels (1999), as in this view the activity level of V5 should directly determine whether moving percepts are perceived. It is also inconsistent with the theory of Hochstein and Ahissar (2002) as in their account awareness is viewed as a continuum between the activation of extrastriate areas and the backprojections to V1. For this theory to hold, the activation level of both V1 and V5/MT should determine whether moving percepts are perceived. Furthermore, in their view disruption to V1 would remove fine details from the percept, but a percept of some kind should nevertheless be perceived. It remains to be seen whether the findings reported here apply to the conscious perception related to activity in other extrastriate areas.

7.3. The modulation of V5 activation by frontal eye fields

The findings described in Chapter 6 provide a more complete picture of the interactions in the visual cortex that give rise to visual awareness. As information enters the visual system, the frontal eye fields are activated by subcortical pathways (Raiguel et al, 1995) at similar latencies at which information reaches V1, and this activity already plays a role in determining whether a target is perceived (Thompson & Schall, 1998). Furthermore, a recent TMS study has demonstrated the necessity of this early FEF activity in visual detection (O'Shea et al, 2004). In this study, TMS applied over human frontal eye fields 40-80 ms but not at later time windows after stimulus onset disrupts visual target discrimination (O'Shea et al, 2004). How does this early and necessary activity period in FEF link to the processing in the occipital visual areas that was studied in the Chapters 3 and 4? The results of Chapter 6 can, to an extent, provide an answer to this question. It was demonstrated that stimulation of frontal eye fields prior to induction of phosphenes from V5/MT lowers subjects' phosphene threshold and thus facilitates awareness of V5/MT activation. This finding and its time course (with a preceding but not a postdating FEF pulse lowering the phosphene threshold of V5/MT)

imply that projections from the FEF to the visual cortex increase the activation level of neurons in which they terminate. The FEF can thus modulate visual awareness of V5/MT activation: ehancement of V5/MT activity also facilitates the backprojections from V5/MT to V1, increasing the likelihood that information contained in V5/MT reaches awareness. In real vision, the projections from FEF to the visual cortex would selectively enhance the neurons responding to target features, thus making it more likely that the target stimulus is consciously perceived.

The effect of FEF on visual cortical activity level have been previously shown in the monkey (Moore & Armstrong, 2001), but the present results are the first to directly link projections from FEF to visual cortex to facilitation of visual awareness. Furthermore, the evidence from the monkey literature involves connectivity between the FEF and ventral stream area V4, whereas these results demonstrate FEF's functional connectivity with a dorsal stream region.

7.4. Conscious perception in subject in the absence of V1

The objective of experiments described in Chapter 5 was to investigate whether the intact hemisphere in the blindsight subject GY can enable conscious perception of activation in the extrastriate cortex of the lesioned hemisphere, if information transfer between the two hemispheres is artificially facilitated. This was done by applying transcranial magnetic stimulation (TMS) over the contra- and ipsilesional V5/MT in close temporal proximity.

In agreement with an earlier result (Cowey and Walsh, 2000) GY perceived phosphenes in his normal, left, visual hemifield when TMS was applied to his right V5/MT but never perceived a phosphene in his blind hemifield when TMS was applied to V5/MT of his damaged hemisphere. In striking contrast he experienced bilateral phosphenes when the area V5/MT was stimulated bilaterally. This is the first report of visual qualia in the blind field of a blindsight subject and it has implications for the view that V1 is necessary for conscious perception.

At least two explanations can be offered for this finding. Firstly, it is possible that the intact V1 can compensate for the lack of ipsilesional V1 in allowing activation in the ipsilesional V5/MT to reach awareness. The abnormal functional connectivity between the ipsilesional V5/MT and contralesional V1, reflected in the effect of ipsilesional V5/MT TMS on phosphenes induced from the contralesional V1, offers some support for this view. A representation of the ipsilateral visual field exists in the visual cortex (Zeki, 1974, Raiguel et al, 195) and it is likely that the ipislateral representation in GY's intact hemisphere mediates his blind field perception.

However, it is not clear why the ipsilateral representation in GY's intact hemisphere is unable to mediate conscious phenomenal perception of visually presented stimuli, given that it does obtain activation from the damaged hemisphere (ffytche et al, 2001). Furthemore, the finding that GY perceived phosphenes in his blind field even when the ipsilesional stimulation postdates the contralesional stimulation (and not only when the ipsilesional stimulation precedes contralesional stimulation) might seem inconsistent with this explanation. This is because in order for the ipsilesional activation to be tagged on to the process that gives rise to consciousness, its activation needs to be projected to the contralesional hemisphere before the latter is activated by TMS. However, the ipsilesional V5/MT TMS did influence the appearance of the contralesional V1 phosphene also when its stimulation preceded the latter. It seems that the temporal aspects of cortico-cortical interactions are abnormal in GY's visual cortex and cannot be used to infer, as can be done in normal subjects, the flow of activation that gives rise to conscious perception.

A second possibility is that it is the interaction between the two V5/MT's that enabled conscious perception in GY's blind field, without the contralesional V1 playing any part. In this account, there is nothing unique about V1; rather, it is cortico-cortical interactions between any two visual areas that give rise to visual awareness. This begs the question of why is conscious perception lost after V1 damage. An obvious possibility is that size and computational power of the largest visual area is, under

normal circumstances, necessary for visual awareness, and that only an artificial enhancement of recurrent activity between two extrastriate areas enables conscious perception to arise in the absence of V1. However, the abnormal functional connectivity between the ipsilesional V5/MT and contralesional V1 argues against this possibility and instead suggest a role for the contralesional V1.

At first sight it appears that the GY's ability to perceive phosphenes in his blind field is at odds with the findings described in chapters 3 and 4. On a closer inspection, however, this is not necessarily the case. Chapter 3 demonstrated that backprojections from V5/MT to V1 are necessary for conscious perception of real, visually presented motion stimuli, and consistent with this, there is no evidence that G.Y. can be aware of real, visually presented motion stimuli; he cannot even perceive phosphenes when TMS is restricted to his ipsilesional hemisphere.

The findings presented in Chapter 4 demonstrated that activation level of V1 determines whether phosphenes induced from V5/MT are perceived. However the findings with GY clearly demonstrate that an intact ipsilateral V1 is not necessary for conscious perception of simple visual qualia induced by stimulation of the extrastriate cortex. It is clear that additional qualifications are necessary to the conclusions made in Chapter 4. As was discussed above, it is possible that awareness can arise as a result of cortico-cortical interactions between any two visual areas. A prediction of this is that in normal subjects subthreshold V1 stimulation does not disrupt the perception of moving phosphenes if V5/MT is stimulated bilaterally, as is the case with unilateral V5/MT stimulation (cf Pascual-Leone & Walsh, 2001). In other words, there are many interactions that can potentially give rise to awareness.

Whether the finding that GY can perceive visual qualia in his blind field is inconsistent with the two extreme theoretical viewpoints depends on the neural basis of GY's phosphenes. On one hand, the fact that stimulation of the contralesional V5 is required to induce conscious percepts in GY blind field is inconsistent with the microconsciouness theory (Zeki & Bartels, 1999), as it would predict that stimulation of

the ipsilesional V5 by itself should be sufficient. On the other hand, the fact that GY can perceive phosphenes at all implies that an ipsilateral V1 cannot be necessary for conscious perception of extrastriate activation (Lamme, 2001), unless an abnormal functional connectivity with the contralesional V1 has developed. This issue cannot be resolved without a clear knowledge of the neural correlates of GY's blind field percepts.

7.5. Future directions

Whether the importance of extrastriate – V1 feedback activity extends beyond motion perception is not known. All the evidence so far has come from studies that have looked at the information exchange between V5/MT and V1 in motion perception, and in order to determine whether these findings reflect a general process in which visual information reaches awareness, the cortico-cortical interactions between V1 and other extrastriate areas, particularly within the ventral stream, need to be examined. This can be studied by investigating the role of V1 in conscious perception of phosphenes induced from various extrastriate areas, using the technique of Pascual-Leone & Walsh (2001) and the experiments described in Chapter 5, as well as and in relation to conscious perception of visually presented shapes and colour, using the methods used in experiments described in Chapter 3. Furthermore, real vision often requires binding of attributes such as colour and motion, and future experiments should investigate how feedback connections from various extrastriate areas into V1 interact in such circumstances.

It also needs to be determined whether feedback from the motion area V5/MT to V1 is necessary for conscious perception of all types of motion stimuli. The stimuli that were used in this study were less than one degree of visual angle in size and it has been suggested that feedback activity in V1 might be particularly important with such fine-detailed stimuli (Pollen, 1999; Hochstein & Ahissar, 2002). This can be addressed by determining whether increases in speed and size of the moving targets will diminish the importance of feedback activity in V1. The limitation to such an experiment is the area

of V1 affected by a TMS coil, but stimuli that are at least twice the size of motion displays used in Chapter 3 could be used.

A more fundamental issue involves whether awareness of basic qualia requires extrastriate-striate backprojections specifically, or whether recurrent activity between any two visual areas is sufficient. Turning visual input into a conscious percept seems to require V1, as is implied the fact that GY does not experience qualia when stimuli are presented to him visually. This could be tested by stimulating V5/MT bilaterally in normal subjects to induce bilateral phosphenes and then to study whether this percept is disrupted by applying a subthreshold pulse over V1. However, this line of research is only useful if GY's contralesional V1 is not responsible for his blind field phosphenes.

Future studies also need to determine whether subjects with bilateral V1 damage can perceive phosphenes. Also, the role of the contralesional V1 in generating blind field phosphenes in GY needs to be conclusively determined. This issue can be resolved by combining TMS with functional neuroimaging: by comparing the fMRI or EEG response of bilateral vs. good field phosphenes in GY it would be possible to infer which brain regions are selectively activated when GY perceives phosphenes in his blind field.

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